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VENTRICULAR HEMORRHAGE: A SYMPTOM-GROUP*

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PHILADELPHIA

Hemorrhage in the brain may be extraventricular or intraventricular. In the latter case the blood may originate in the ventricle itself and produce a primary ventricular hemorrhage. In the first, the original seat of the hemorrhage is the tissue surrounding the ventricle and the ventricle itself is only secondarily involved. Secondary effusion of blood into cerebral ventricles is not an infrequent phenomenon, while a primary hemorrhage within the ventricular cavity is rather a rare occurrence, judging from the meager literature on the subject. Not many records are to be found on primary intraventricular hemorrhage. Nevertheless, sufficient data have been accumulated to deserve a special description.

The mechanism of formation, the pathology, the course, the symptomatology of ventricular hemorrhages have been somewhat differently considered by various authors who have had the opportunity to observe such findings. All writers, however, concur in the belief that this form of cerebral hemorrhage is quite infrequent. In view of this infrequency it may be of interest to place on record twelve personal cases of extraventricular and intraventricular hemorrhage studied from anatomical and clinical standpoints. The study of this series suggests a remarkable uniformity in the pathological aspect and in the manifestations during the patients' lives, so that diagnostic inferences appear to be admissible.

Out of the twelve cases seven presented secondary effusion into the ventricles from an original extraventricular area situated close in the vicinity of the cavity. The remaining five cases are examples of primary intraventricular hemorrhage.

I propose to consider first the latter group and the mechanism of formation of the hemorrhage before several other interesting features.

PATHOLOGY

In Cases 2 and 3 sections of the brains were made on the third day of hardening; the blood was washed out thoroughly from the lateral

* Submitted for publication Nov. 12, 1915.
* From the Neuro-Pathological Laboratory of the Mt. Sinai Hospital.

ventricles and the source of bleeding could be distinctly seen in the choroid plexuses. The choroid plexuses have been considered by many observers as the principal source of intraventricular hemorrhages. From the time of Morgagni, who uniformly considered those plexuses as being the unique source of the bleeding, up to the present time, the majority of observers believe that even in cases in which the seat of the bleeding could not be discovered, the blood vessels of the choroid plexuses are the origin of the ventricular hemorrhage. Degeneration, chronic inflammation, fatty changes, calcareous deposits, dilatation—all these conditions have been observed in the vessels of the plexuses. Thrombosis, aneurisms of the blood-vessels, angiomatous tumors and cysticerci attached to the plexuses have been observed in a few cases (Broca). Serous cysts originating in the walls of the blood vessels have been found in aged individuals also in cases of atrophy of the brain (Wilks). In the Cases 2 and 3 in which rupture of vessels of the plexus was present, the vessel wall showed fatty degeneration and rounded yellowish masses were seen in the posterior portions of the plexus. These masses were very likely remains of former blood effusions. In all of them pronounced changes were evident in the intima, such as disappearance of the endothelium, degeneration and thickening. The elastica interna usually followed the changes of the intima. The adventitia was found thickened in some vessels, but the media was frequently seen altered, viz., granular and calcareous masses were present. Some vessels were greatly distended with blood, but not to the extent of formation of aneurysm. On none of the sections could a true or false aneurism be detected.

In Cases 1 and 4 after the blood was washed out erosion of the ventricular walls could be seen. Here the blood vessels were found enlarged and distended with blood. Some of them showed calcareous deposits; in others complete occlusion with thrombi was evident. Both individuals were of somewhat advanced age, one 63 years old, the other 67. The ulcerations mentioned were seen on the wall of the corpus striatum in the lateral ventricle.

Case 5 is most interesting from the standpoint of pathogenesis. Nothing abnormal could be found macroscopically, but under the microscope very small aneurysmal enlargements could be seen.

As is well known, miliary aneurysms were considered by Charcot and Bouchard as the chief cause of cerebral hemorrhage. Before them distention of blood vessels and aneurysms were mentioned as causes of cerebral hemorrhage. But since these two observers published their monograph in 1868, the subject of miliary aneurysms was indiscriminately emphasized as being the sole etiologic factor. In their collection of eighty-four cases of cerebral hemorrhage, in all of them multiple

miliary aneurysms were found. In their study they confined themselves to gross pathological changes. They placed the brains in water and small floating masses of tissue with their vascular attachments were picked out and examined under magnifying glasses.

Fig. 1.—Primary intraventricular hemorrhage (in lateral cornua on right). Note deviation of the opposite side. Patient operated on.

The subsequent writers on the subject studied miliary aneurysms from the histological standpoint. The intima, the adventitia and the muscularis have all or individually been considered as the origin of aneurysmal dilatation of the blood vessel. Lowenfeld[1] from a study

1. Lowenfeld: Studien über Aetiologie u. Pathogenese der spontanen Hirnblutungen, Wiesbaden.

of seventeen brains, all with miliary aneurysms, found in every one the three vessel coats perfectly intact. The weight of opinion of the majority who believe in the existence of miliary aneurysms, however, is that the changes begin first in the media. The latter degenerates, becomes atrophic, the entire vessel wall becomes then nonresistant, and aneurysmal dilatation follows. This condition occurs especially in the very small cerebral arteries. In a large number of cases no miliary aneurysms were found and the rupture of the blood vessels was due to a diffuse degeneration of their walls. Kaufman,[2] for example, finds atheromatous changes in the large cerebral blood vessels and hyaline degeneration in the small ones.

Finally, the existence itself of miliary aneurysms is disputed by some writers.

In my case, after a thorough washing of the hemorrhagic lateral ventricle the brain tissue on the inner wall was seen torn and a number of exposed small vessels could be noticed. Portions of the lacerated tissue were placed in water so as to enable me to observe the blood vessels. Some of them were irregular and projections were seen on their walls. The remainder of the tissue was hardened in Müller's fluid and later examined microscopically. Imbedding was done in celloidin. Staining was done with osmic acid, Weigert's hematoxylin and ammonia carmin. Sections were made longitudinally and perpendicularly to the vessel. Marked changes of the intima and the elastica were found on many sections. Rupture of the intima and blood placed between the latter and elastica were seen on some sections. Swelling of the intima, disappearance of the endothelium, and hyaline appearance of the elastica could also be seen. Lesions of the media were always seen in conjunction with lesions of the intima; degeneration or calcareous deposits, thickening, were observed in the latter. The adventitia was seen split in one or two layers with blood between them. In the aneurysmal dilatations no clear distinction could be made of the individual membranes of the vessel wall. The latter consisted only of a few thin bands infiltrated with leukocytes. The aneurysms were filled with blood and in some sections blood was seen immediately around the vessel. In the latter cases the opening of the ruptured vessel could be traced. A gradual transition from the vessel wall to the aneurysm was noted. In all cases the changes of the intima become more and more marked as the aneurysmal sac is approached. In a number of sections the so-called dissecting variety of aneurysms could be seen, viz., a sacular dilatation of the vessel was present and blood had penetrated between the intima and the media or media and adventitia.

2. Kaufman: Specielle Pathologic Anatomie, 1907.

The histological findings in all the five cases permit the conclusion that as far as the mechanism of formation of the hemorrhage is concerned, the latter may be produced by simple rupture of the vessel wall or of a miliary aneurysm, but in both cases profound changes of some or all layers of the wall are always present and especially more pronounced in the intima.

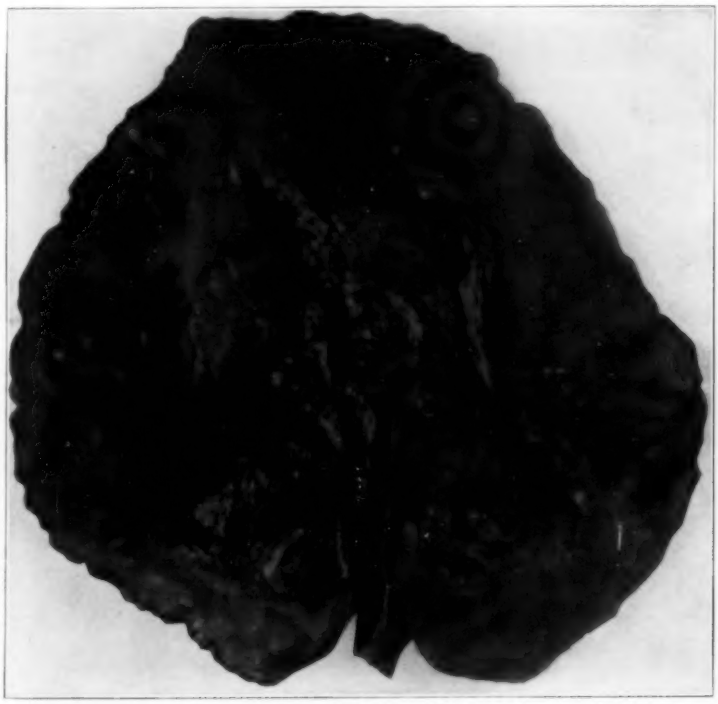

Fig. 2.—Primary intraventricular hemorrhage (on right, three cornua involved). Note deviation of the opposite side.

The seat of the primary intraventricular hemorrhage, as seen from my five cases, is distributed as follows: Two cases in both lateral ventricles; in one of them blood was found in the three cornua of one ventricle and only in the anterior and posterior cornua of the other ventricle; in the second case the hemorrhage was seen in all the cornua of one ventricle and only in the posterior cornua of the other ventricle. Three cases presented hemorrhage in one lateral ventricle; in four out

of five cases the right lateral ventricle seems to be the predominant seat of hemorrhage. In only one case was the hemorrhage seen exclusively in the left lateral ventricle.

The seven cases of secondary ventricular hemorrhage present this peculiarity, that here hemorrhage in both lateral ventricles was seen in a larger number (five) than in cases of primary ventricular hemorrhage.

The blood in the ventricles was found coagulated in four cases and fluid in one case. In the latter, death ensued instantaneously. In the former in six, seven, twelve and twenty-four days, respectively. The patient in the latter case was operated on (see below) and at necropsy a firm clot was found. It is interesting to note that in the unilateral cases the ventricle which was free from blood was filled with serous fluid. The walls of the ventricles presented small erosions in three cases. In two cases with diseased blood vessels of the choroid plexuses, the ventricular walls were intact. It is to be presumed that the lacerated face of the ventricles was the result of the diseased vessels and of miliary aneurysms which eventually ruptured. Under the microscope destruction of tissue was seen, but there was no indication of a degenerative state which usually follows softening. The remainder of the brain with its meninges was intact.

In all the five cases the brain tissue in the immediate vicinity of the hemorrhage suffered destruction. In three cases the hemorrhage, besides destroying the surrounding brain tissue and pushing outward the remaining cortical substance, exercised also considerable pressure on the opposite hemisphere and disfigured it. This latter fact, observed at first in one case, suggested a certain surgical procedure for relief of increased intracranial pressure which will be discussed later. In the two other cases the hemorrhage was bilateral so that no marked displacement of brain substance to one or to the other side could be observed.

The pathology of the second series of my cases, seven in number, presents no special features deserving special mention. The original hemorrhage occurred in all in the internal capsule and inundated secondarily the lateral ventricles. Bilateral hemorrhage was present in five out of seven cases. In the two unilateral cases the right lateral ventricle alone was involved. In three cases were found degenerative changes of blood-vessels, especially of the intima, such as was described in the cases of primary ventricular hemorrhage. In four cases multiple miliary aneurysms were seen in the seat of original bleeding. The technic as to preparing the tissue hardening and staining was exactly the same as in the first series.

DIFFERENTIAL CLINICAL FEATURES

The most interesting manifestations in the primary ventricular hemorrhages of my five cases were: the sudden onset; the most profound coma from the very beginning; convulsions more marked on the side opposite to the lesion than on the same side in the unilateral

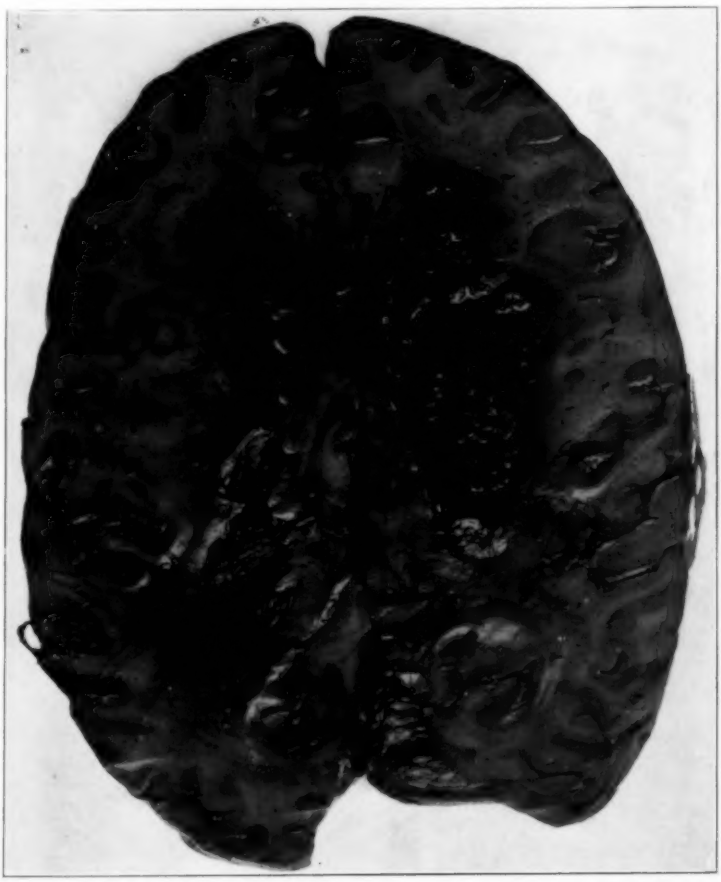

Fig. 3.—Primary intraventricular hemorrhage (both lateral ventricles).

cases, and on the side opposite to the seat of the largest hemorrhage in the bilateral cases; finally, absence of marked paralysis—the latter was very slight. These four symptoms were uniformly present in all the five cases at the time when the attack was ushered in.

During the comatose state two patients with unilateral hemorrhage had several convulsive seizures, always contralateral; the other three patients had but one initial attack. The most striking phenomenon is the absence of true paralysis. At first similarly to ordinary cerebral hemorrhage, the sudden loss of power was evident, but subsequently during the patient's short life the usual rigidity and contracture did not appear. The absence of rigidity is quite interesting, as since Durand-Fardel, early contracture of th_ limbs had been considered pathognomonic of primary intraventricular hemorrhage.

Loss of power is very slight. The latter becomes especially evident where the patient attempts in his comatose state to move his limbs or when he defends himself against external stimulations. As to the reflexes, the knee-jerk on the paralyzed side was not especially increased, although it was somewhat greater than on the normal side. Ankle-clonus was absent, the toe phenomenon was also absent: stimulation of the sole provoked no movement of the toes at all, neither was there any response of the toes with the test for the paradoxical reflex.

In the cases of secondary ventricular hemorrhage the already existing paralysis and contracture became markedly accentuated at the time the ventricles were invaded. The abnormal reflexes which are usually present in hemiplegias were manifest here. All these patients were comatose at the time of the ventricular attack and never regained consciousness during their remaining short life. Among other distinguishing although not constant features of primary ventricular hemorrhage may be mentioned the character of the premonitory symptoms and the duration of the comatose state.

In three of my five patients the attack was ushered in without the least preceding objective or subjective disorder. One patient complained for a few hours of a slight headache, and another patient of a slight vertigo during two preceding days. The attacks consequently bear no relation to the existence or nonexistence of premonitory symptoms. Two of the patients were aged individuals, above 60, and presented evidences of arteriosclerosis; three were of middle age without apparent arterial changes.

The character and duration of the coma are of interest. The latter appeared at the commencement of the seizure, remained complete throughout the short life. In the secondary ventricular hemorrhage the coma was also present with the irruption of the blood into the ventricle. Therefore the mere existence of unconsciousness is of little value in differential diagnosis. It is the sudden onset of profound coma without preceding hemiplegia that will determine the diagnosis of a primary hemorrhage in the ventricle.

In the series of secondary ventricular hemorrhage, death followed but a few hours after the inundation of the ventricle in every case. In the cases of the primary variety, with one exception of instantaneous death, life persisted from six to twenty-four days. The latter patient was operated on, which probably accounts for the longest duration. The subject will be discussed later. The other three patients lived

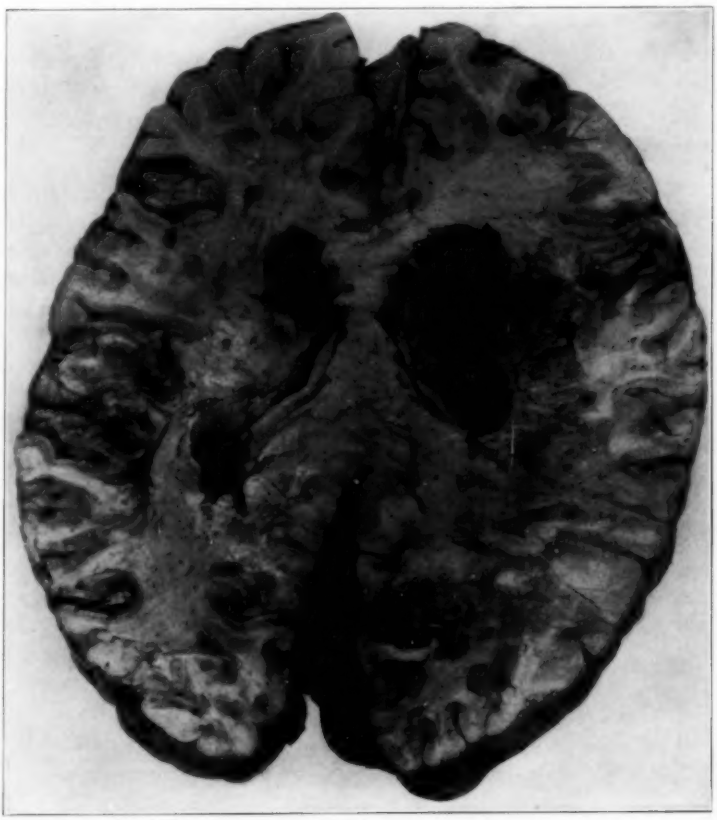

Fig. 4.—Primary intraventricular hemorrhage (on right).

though unconscious six, seven and twelve days, respectively. The seat and the size of the hemorrhage have no direct relationship to the duration of life. Thus, in Case 3 the hemorrhage was more extensive than in Case 4. Nevertheless, the former lived twelve days and the latter but six days. On the whole it seems that the fatal issue is less rapid in the primary than in the secondary variety of ventricular hemorrhage.

A rapid glance at the brains in the five cases of primary ventricular hemorrhage shows displacement of the brain tissue to the side opposite the blood in three cases, and consequently the possibility of the comatose state as due to sudden undue pressure on the normal side of the brain appeared to be highly plausible. Such a finding in one case suggested the idea of surgical intervention in other cases with the object of relieving the intracranial pressure on the sound side. Accordingly an attempt was made in one case for a decompressive operation. Although the patient (a woman of 45) did not recover eventually, nevertheless the duration of her life was prolonged to twenty-four days. Immediately after the operation there was a decided improvement in her respiration, in response to external stimulation, in the cardiac action. For several days she could open her eyes voluntarily and when called by her name; she could be fed more readily than before, as she would respond to requests to open her mouth, and she could swallow. On the twentieth day the coma returned and on the twenty-fourth day she expired. The improvement obtained was undoubtedly due to the relief of the intracranial pressure. Unfortunately the operation was consented to only on the fifth day after the apoplectic seizure, viz., after five days of a comatose state. Efforts were made to operate in the other four cases, but permission could not be obtained.

SUMMARY

The present study suggests the following interesting features in primary intraventricular hemorrhage:

1. From a diagnostic standpoint sudden onset without premonitory symptoms, profound coma at the outset and continuing for several days without improvement, absence of genuine paralysis, absence of rigidity and contracture during the days following the seizure, absence of the toe phenomenon—all of these manifestations speak in favor of primary ventricular hemorrhage.

It should be borne in mind that in all the five cases the hemorrhage occurred only in the lateral ventricles. The above mentioned phenomena were observed in but five cases. The number is too small to draw general conclusions. Nevertheless they appeared sufficiently uniform to permit the possibility of their pathognomonic nature, at least in cases when hemorrhage occurs in the lateral ventricles alone.

2. The next important feature of the subject is the surgical intervention on the sound side based on the existence of a displacement of the brain to that side. It is possible that the profound comatose state is due precisely to the sudden compression of the normal brain tissue. The amount of improvement obtained in one case was a sufficient encouragement in that direction. If a decompressive operation on the

sound side is to be undertaken, it must be done promptly after the onset. In my case the operation was performed on the fifth day and in spite of this delay some amelioration of the condition was decidedly

Fig. 5.—Primary intraventricular hemorrhage (both lateral ventricles).

manifest. It is to be presumed that the earlier relief from intracranial pressure is obtained, the more prolonged the favorable results that will be observed.

1812 Spruce Street.

THE GASTRIC MUCOSA IN DELIRIUM TREMENS*

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In the experience of Dr. E. R. Le Count, coroner's physician in Chicago, petechial hemorrhages in the stomach lining are among the most constant lesions found in the bodies of persons dying during the acute delirium of chronic alcoholism. This condition has been considered an acute alcoholic gastritis, but in the absence of any microscopic examination of similar lesions, the nature of these changes was called in question. The present study, therefore, was taken up with the view of determining the microscopic appearance of these hemorrhages, and to see if they actually are a part of an acute inflammation.

Kayser[1] in a report of the gross anatomic changes in the bodies of 120 persons dying with delirium tremens, mentions thirteen instances of hyperemia or ecchymoses in the sixty-nine bodies in which changes in the stomach were noted. An inquiry into the literature for microscopic studies on the stomach in chronic alcoholism disclosed only a few such investigations, with very little comment on the condition of the organ in delirium tremens. On the whole, the stomach condition, where it has been mentioned, is dismissed with the gross descriptive term of "chronic gastritis," without further inquiry into the character of the microscopic picture. In all of the reported examinations of the stomach in chronic alcoholism there is no record of hemorrhages in the gastric mucosa. The omission of a microscopic examination of the gastric mucosa is not surprising when the difficulties of obtaining freshly fixed material are appreciated, and unless the stomach tissue is removed almost immediately after death, autodigestion occurs so rapidly as to make useless an histological study.

In the experimental studies on the influence of alcohol on lower animals some interesting changes have been noted in the stomach. Kremiansky,[2] working with dogs, observed a slight catarrhal inflammation of the stomach and bowel, manifested by an edema, thickening, and

* Submitted for publication, Nov. 9, 1915.

* From the Laboratories of Pathology of Rush Medical College and the University of Chicago.

1. Kayser, O.: Ein Beitrag zur Alkoholfrage, I.D., Kiel, 1888.

2. Kremiansky, J.: Ueber die Pachymeningitis interna hemorrhagica bei Menschen und Hunden, Virchows Arch. f. path. Anat., 1868, xlii, 321.

slight pigmentation. Ruge,[3] after introducing alcohol into the stomachs of dogs through a tube, found hyperemia of the mucosa in some, ecchymoses in one, blood-stained feces in another, and marked swelling of the gastric mucosa in a third. No changes were seen in the tissues of rabbits receiving alcohol subcutaneously from four to thirteen days. During an experimental study of alcoholic liver cirrhosis in rabbits, Straus and Blocq[4] found changes to a greater or less degree in all stomachs. In the stomachs of those animals dying within the first days or weeks there were erosions and hemorrhages; of those surviving a longer period of experimentation there were either healed or nearly healed ulcers. The mucosa of the latter was pale, thickened, and generally covered with mucus. Naturally, as Quensel[5] suggests, the mechanical effect of the stomach tube in these experiments must be considered. Microscopically, the gastric mucosa of these animals was infiltrated with round cells. Dujardin-Beaumetz and Audige[6] observed hyperemia of the alimentary tract with occasional hemorrhages. Afanassijew,[7] after introducing alcohol into the stomachs of dogs, rabbits, guinea-pigs, and rats, found a marked increase of the mucous secretion, and a considerable hyperemia of the mucosa. Occasionally extravasations of blood were present in the mucosa of dogs' stomachs, lesions rarely seen in the stomachs of rabbits. Microscopically these hemorrhages in the gastric mucosa were of variable size, sometimes extending through the entire width of the mucosa, and covering a considerable surface area. From a very limited experimental series (two dogs), Chretien[8] concludes that alcohol produces in the dog a chronic gastritis with the formation of cysts and a return of the mucosa to an embryonic state. These changes, he says, correspond with those described under the name "mucous gastritis." Braun,[9] feeding rabbits and dogs with alcohol for a considerable period of time, could not confirm the changes described by Afanassijew. In several rabbits he observed stomach erosions and recent hemorrhages, which he thinks

3. Ruge, P.: Wirkung des Alcohols auf den thierischen Organismus, Virchows Arch. f. path. Anat., 1870, xlix, 252.

4. Straus and Blocq: Etude expérimentale sur la Cirrhose alcoolique du Foie, Arch. de Phys. norm. et path., 1887, x, 409.

5. Quensel, Ulrik: Alkoholfragan fran Medicinsk Synpunkt. Uppsala and Stockholm, 1913.

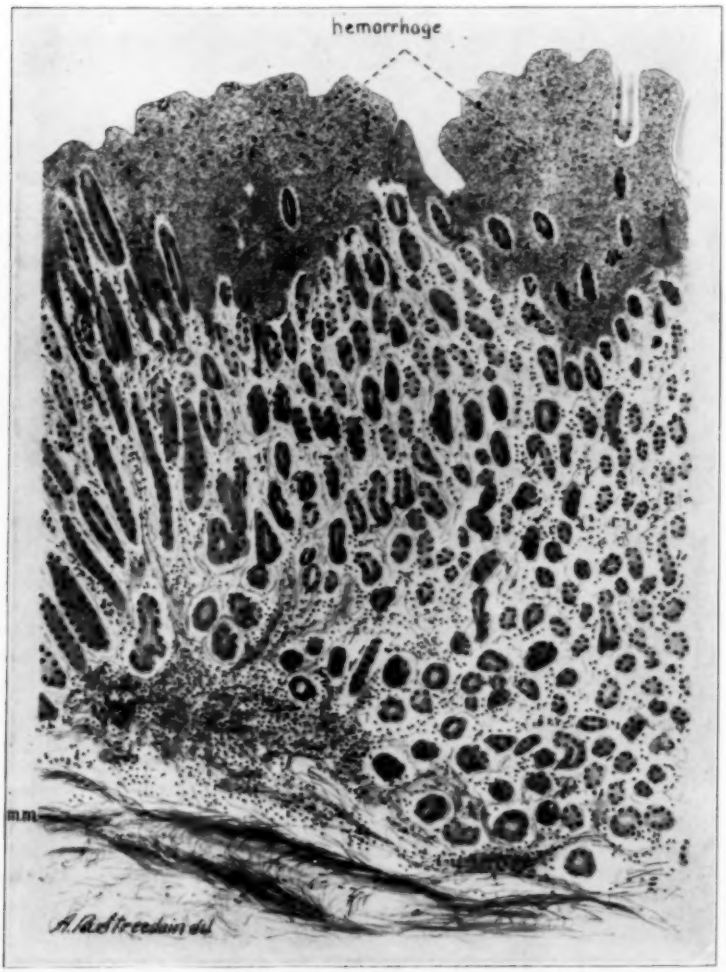
6. Dujardin-Beaumetz and Audige: Recherches expérimentales sur l'alcoolisme chronique, Compt. rend. de l'Acad. d. Sc., 1883, xcvi, 1557.

7. Afanassijew, W. A.: Zur Pathologie des acuten und chronischen Alkoholismus, Ziegler's Beitr., 1891, ix, 349.

8. Chretien, M.: Sur les Altérations de la Muqueuse gastrique et les modifications du Chimisme sous l'influence de l'ingestion prolongée d'Alcool. Thèse Lille, 1897.

9. Braun, H.: Ueber die experimentelle durch chronische Alkoholintoxication hervorgerufenen Veränderungen in zentralen und peripheren Nervensystem. Inaugural Dissert., Tübingen, 1899.

resulted from the alcohol, this having been given in rather high concentrations. Baumgarten[10] gave alcohol to rabbits by mouth and subcutaneously. With both methods of administration he observed



Low power sketch locating the hemorrhages in the gastric mucosa, and illustrating the absence of acute inflammation about them.

10. Von Baumgarten: Ueber die durch Alkohol hervorgerufenen pathologisch-histologischen Veränderungen, Verhandl. d. Deutsch. Path. Gesellsch., 1907, xi, 229.

numerous hemorrhagic erosions of the gastric mucosa. Since the mechanical factor is absent in animals receiving alcohol subcutaneously, Baumgarten believes that the stomach lesions are not produced mechanically, but that they have some relation to the alcohol action, probably being the result of some vascular disturbance, such as a vasomotor spasm producing an anemic necrosis on which the gastric secretions act. D'Amato[11] observed in the stomachs of two dogs daily receiving alcohol over a period of three and a half months, hyperemia, parenchymatous and interstitial inflammation. Fahr,[12] experimenting with guinea-pigs and rabbits for long periods, observed no changes in the stomachs of the guinea-pigs, but in those of the rabbits he noted a distinct reddening. Microscopically there was nothing abnormal.

From this brief review, in which no attempt is made to collect all the experimental data concerning the effect of alcohol on the stomach of animals, there is noted a considerable divergence of observed conditions. Quensel does not think a clear and definite picture of the effect of alcohol on the stomach wall is possible from these studies. As is well known, alcohol in strong concentrations acts as a caustic on the gastric mucosa, and inasmuch as some experimenters gave alcohol in this form, an explanation for their findings seems probable. However, such strong alcohol is rarely used by chronic alcoholics.

To obtain material satisfactory for miscroscopic study, Zenker's fixing fluid was introduced into the stomach by means of a stomach tube immediately after death. During the postmorten examination later, portions of the fixed stomach were removed and preserved in alcohol. Of the twenty-one stomachs examined in this way, nine are from bodies that anatomically confirmed the clinically diagnosed delirium tremens; the other twelve stomachs are from the bodies of persons dying from various other disorders, some having been chronic alcoholics for many years. The latter group serves as a comparative control in this study. For the microscopic study, small pieces of tissue from both the anterior and posterior walls, respectively, in the pyloric, fundic, and cardiac regions of each stomach, were embedded in paraffin, sectioned, and stained with hematoxylin and eosin in the usual way. Thus large series of sections were prepared with tissues taken from six different regions of each stomach, making possible a careful examination.

11. D'Amato, L.: Ueber experimentelle vom Magendarmkanal aus hervorgerufenen Veränderungen der Leber und über die dabei gefundenen Veränderungen der übrigen Bauchorgane, Virchows Arch. f. path. Anat., 1907, clxxxvii, 435.

12. Fahr: Beiträge zur Frage des Chronischen Alkoholismus, Virchows Arch. f. path. Anat., 1911, ccv, 397.

Table 1 contains the histological report of the delirium tremens stomach with a brief statement of the cause of death, and some clinical and anatomic notes of interest. Table 2 contains similar data for the stomachs studied as controls.

The mucosa of all the stomachs removed from persons dying with delirium tremens contains hemorrhages of varying dimensions. The largest are easily recognized with the unaided eye, while the smallest are microscopic in size. All of these hemorrhages lie in that portion of the mucosa immediately adjacent to the stomach lumen, and none is found in the deeper portion, nor in the submucous or muscular layers. Microscopically, the smallest hemorrhages are minute areas of tissue edema with a small number of red blood corpuscles lying free in the interstitial tissue spaces. The larger ones are extensive collections of red blood cells closely packed into the tissues of the mucosa. There are no polymorphonuclear leukocytes either among the red corpuscles in these hemorrhages or in the surrounding tissues. In fact, the absence of changes indicating acute or chronic inflammatory processes is striking. Only a few widely isolated, small collections of polymorphonuclear leukocytes in and about some of the stomach tubules have been observed, and these without exception have had no relation with the hemorrhages described.

There are no hemorrhages in the mucosa of the stomachs used in this study as comparative controls, except those in which death was accompanied by or resulted from an acute toxic condition.

Excepting for the presence of hemorrhages, the stomach in delirium tremens is unaltered to any great extent. This is of especial interest, inasmuch as chronic alcoholism frequently is said to produce a chronic catarrhal gastritis. In only three of the twenty-two stomachs examined is there any microscopic evidence of a mucoid degeneration of the epithelium, and comparison with tissues used by Bensley[13] in describing the normal histology of the stomach revealed no striking alteration excepting as mentioned.

The occurrence of petechial hemorrhages in the gastric mucosa of persons dying in delirium tremens affords additional evidence on which a gross anatomic diagnosis of this disorder may be made. In the absence of acute toxic processes accompanying death, the presence of multiple petechial hemorrhages in the stomach lining is of great significance, and when taken into account with the clinical and other anatomic data, affords a substantial basis for ascribing the cause of death to delirium tremens. Kayser's report of anatomic changes in delirium tremens is simply a tabulation of changes present in the bodies

13. Bensley, R. R.: Ref. Handb. Med. Sc., 1904, (7), 461.

TABLE 1.—DATA CONCERNING DELIRIUM TREMENS STOMACHS

No.	Microscopic Study of Gastric Mucosa	Cause of Death	Clinical and Anatomic Notes
1.	Large hemorrhages in the fundus and cardia	Delirium tremens	Aged 30. Came to the hospital irrational; became wildly irrational and died shortly after.
2	Small hemorrhages in the fundus and cardia. Moderate atrophic gastritis	Delirium tremens	Aged 50. Observed one day. Anatomically, delirium tremens.
3.	Very small hemorrhages; marked hyperemia; small collections of polymorphonuclear leukocytes in and about the tubules; moderate atrophic gastritis	Delirium tremens	Aged 52. Observed one day with diagnosis of chronic alcoholism. Had been a chronic alcoholic for 30 years.
4.	Numerous small hemorrhages; marked hyperemia; moderate postmortem changes	Delirium tremens	Aged 29. Observed four days. Was an habitual heavy drinker; irrational when admitted; present bout of a week's duration.
5.	Few small hemorrhages; moderate hyperemia; slight postmortem changes	Delirium tremens	Aged 38. Observed two days. Was irrational when admitted; had been a chronic alcoholic for twenty-three years.
6.	Numerous small hemorrhages; marked hyperemia and edema: small collections of polymorphonuclear leukocytes in and about some of the tubules	Delirium tremens	Aged 44. Observed one day without a clinical diagnosis. Anatomically only delirium tremens.
7.	Widely disseminated small hemorrhages; small areas of mucoid degeneration of the tubular epithelium, and small collections of polymorphonuclear leukocytes about some of the tubules	Delirium tremens	Aged 44. Was a heavy drinker for twenty-four years. Clinically diagnosed delirium tremens. Anatomically had disappearing contusions of the cerebral cortex.
8.	Numerous small, widely disseminated hemorrhages; moderate hyperemia	Delirium tremens	Aged 50. Had been drinking indefinitely when arrested; observed eighteen days; on the second became irrational, and later developed pneumonia. Anatomically pseudolobar bronchopneumonia.
9.	Very small hemorrhages; mucoid degeneration of the glandular epithelium	Delirium tremens	Aged 47. Observed five days with clinically diagnosed delirium tremens and chronic nephritis.

TABLE 2.—CONTROL STOMACHS

No.	Microscopic Study of Gastric Mucosa	Cause of Death	Clinical and Anatomic Notes
1.	Small hemorrhages in the fundus and cardia; moderate atrophic gastritis	Meningitis	Aged 40. Observed two days, irrational when admitted; skull fracture suspected. Anatomically, suppurative otitis media and lateral sinusitis
2.	Moderate edema; marked atrophic gastritis	Skull fracture...	Aged 83. Was irrational when admitted and clinically diagnosed delirium tremens.
3.	Moderate hyperemia and edema; slight atrophic gastritis	Spontaneous hemorrhage	Aged 50. Pachymeningitis hemorrhagica. Clinically diagnosed delirium tremens and lobar pneumonia. Anatomically marked compression of the brain, but no skull fracture found.
4.	Slight edema and hyperemia	Fractured calcaneus (Fat embolism?)	Aged 39. Observed one day; four days before entry fell from a ladder; drank periodically ten to fifteen glasses of whiskey daily.
5.	Small hemorrhages in the cardia	Pulmonary and generalized miliary tuberculosis	Aged 42. Observed one day.
6.	Slight edema and hyperemia	Lobar pneumonia	Aged 22. Lobar pneumonia clinically and anatomically.
7.	Moderate hyperemia and edema; marked postmortem changes	Perirectal abscess; pneumonia	Aged 38. Observed twelve days with clinically diagnosed delirium tremens and lobar pneumonia. Anatomically, burrowing perirectal abscess, pyemia and pneumonia.
8.	Moderate hyperemia and edema; slight mucoid degeneration and atrophy of the gastric glands	Lobar pneumonia	Aged 40. Clinically and anatomically lobar pneumonia.
9.	Moderate hyperemia; small collections of polymorphonuclear leukocytes about some of the tubules; moderate atrophic gastritis	Skull fracture...	Aged 50. Observed thirty minutes. Had been drinking for three days, and on the day before entering the hospital a friend had noticed him acting queerly.
10.	Numerous hemorrhages...	Tuberculous meningitis and peritonitis	Aged 38. Observed six days; history of being an habitual drinker.
11.	Slight hyperemia and edema	Lobar pneumonia	Aged 28. Observed three days under the clinical diagnosis of chronic alcoholism and lobar pneumonia.
12.	Slight hyperemia and edema	Spontaneous (?) subdural hemorrhage	Aged 34. Admitted unconscious and observed one day. Stated he had been struck on the head two days previously; had been drinking. A large subdural blood clot was removed during an operation.

of persons clinically diagnosed as having delirium tremens. This tabulation does not take into account delirium in every way resembling that produced by alcohol, but due to some other entirely different factor, such as meningeal hemorrhage, lobar pneumonia, tuberculous meningitis, skull fracture with sinus thrombosis and acute meningitis, suppurative meningitis, cerebral hemorrhage, trichinosis, bone fractures, icterus, suppurative cystitis and prostatitis, and acute tuberculous peritonitis. These conditions certainly could produce a delirium in every respect resembling that of delirium tremens. The elimination of such doubtful instances of delirium tremens would diminish considerably the number of necropsies reported by Kayser, and would increase materially the percentage of instances in which petechial hemorrhages occurred in the gastric mucosa.

That simply the chronic alcoholism produces the petechial hemorrhages in the stomach lining is not borne out by the repeated examination of the stomachs of chronic alcoholics when such changes are not present in the mucosa. Quensel[5] records an autopsy on a chronic alcoholic, a carpenter by trade, who had used intoxicating liquors in large quantities for a long time. In the stomach, Quensel found a large piece of resin, an indigestible substance contained in an alcoholic solution which the man used in his trade, and which he from time to time had taken as a beverage. Microscopically, only slight changes consisting of some increase in the interstitial tissue were noted. This observation agrees well with the changes noted in the present study where only glandular atrophy and corresponding interstitial tissue changes occurred, these not uniformly present and not necessarily the effect of a chronic alcoholism.

The presence of petechial hemorrhages in the stomach lining of persons dying in delirium tremens affords additional evidence that there is some acute toxic process in this disorder other than the simple alcohol poisoning. In a previous communication[12] this idea was expressed, and while at present the exact nature of this toxic condition remains unknown, it is hoped that further studies will ultimately reveal the basic factors acting in acute alcoholic delirium.

SUMMARY

1. Petechial hemorrhages in the gastric mucosa are among the most common lesions present in the bodies of persons dying in delirium tremens.

13. Hirsch, Edwin F.: A Morphologic and Chemical Study of the Double Refractive Fats of the Adrenals in Delirium Tremens, Jour. Am. Med. Assn., 1914, lxiii, 2186.

2. There is no evidence of any acute inflammation about these hemorrhages, thus leaving no anatomic basis for considering this condition in the stomach an acute alcoholic gastritis.

3. These hemorrhages probably are anatomic manifestations of an acute toxemia.

4. Chronic alcoholism alone is of doubtful etiologic importance in causing chronic gastritis.

My sincere thanks are here expressed to Drs. E. R. Le Count, H. G. Wells, and C. Sceleth for their kind assistance.

THE CIRCULATORY REACTION TO GRADUATED WORK AS A TEST OF THE HEART'S FUNCTIONAL CAPACITY*

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NEW YORK

The valuable aid to diagnosis, prognosis, and treatment which an accurate test of the heart's functional capacity would afford has made it the object of much clinical research, and although a number of tests have been devised, the validity of each has been seriously questioned and no one has met with general acceptance.

As a preliminary to a new form of exercise treatment for cardiac insufficiency which we have described elsewhere, we investigated several of these tests, more particularly one described by Graüpner. The essential features of his test are the deductions made from the form of the curve of the systolic blood-pressure after measured amounts of work. Although we were unable to confirm his most important results, we believe that the method of making frequent readings of the pulse rate and systolic pressure after measured amounts of work furnishes the key to this problem of determining the heart's efficiency.

Our work may be divided into two parts. The first consists in experiments on twenty-three normal persons. In three persons the graduated work was performed by means of a bicycle ergometer of the type described by Krogh and Lindhard,[1] and in twenty persons by means of dumb-bell and bar movements.

The second part comprised experiments on thirty-two patients suffering from cardiac insufficiency. The ergometer was used in two patients, and dumb-bell work in the remaining thirty.

EXPERIMENTS ON NORMAL PEOPLE WITH ERGOMETER

Charts 1 and 2 represent experiments done on a man aged 22 with a normal heart. During work the systolic blood pressure and pulse rate increased and the increase was proportionate to the amount of work done. After work the blood pressure and pulse rate fell rapidly to the original figures, except in the last experiment. In this 2,472 kilogrammeters of work were done in two minutes while the subject

* Submitted for publication Nov. 3, 1915.
* An abstract of this article was read before the Society for Experimental Biology and Medicine, Dec. 15, 1917.
* From the Medical Service of the House of Relief, and the Department of Physiology of Columbia University.

1. Krogh and Lindhard: Skandinavisches Arch. f. Physiol., 1913, xxx, 378.

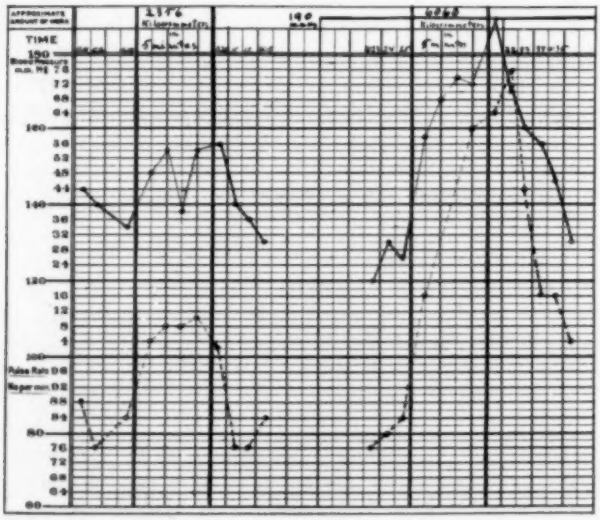

Chart 1.—Circulatory reactions in a normal man to increasing amounts of work performed on the bicycle ergometer. The upper continuous lines represent the systolic blood pressure, the lower dotted lines the pulse rate and the spaces between the heavy perpendicular lines the periods of work in each experiment.

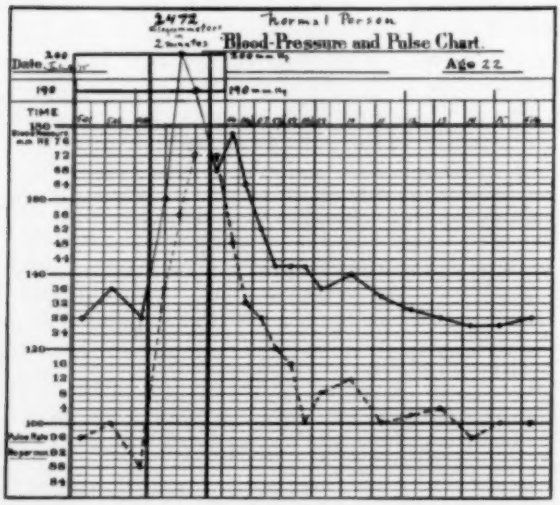

Chart 2.—See Chart 1.

was panting and perspiration was running from his face. Immediately after the work stopped the systolic pressure was 168, and one minute later had risen to 178 at which time the pulse had dropped from 172 to 148. This delayed rise of the systolic blood pressure after heavy work is of much significance and we direct particular attention to it.

Experiments were carried out on two other people with normal hearts with the same results as above, an increase in pulse rate and blood pressure during work and a delayed rise of the systolic pressure following very heavy work.

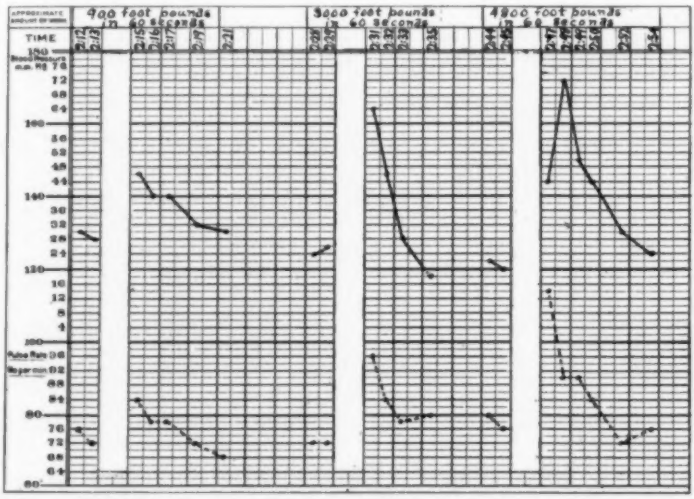

Chart 3.—Circulatory reactions in a normal man to increasing amounts of work performed by means of dumb-bells. The white perpendicular spaces represent the work periods in each experiment during which blood pressure and pulse rate could not be measured.

EXPERIMENTS ON NORMAL PEOPLE WITH DUMB-BELL AND BAR WORK

Various movements with heavy dumb-bells and a steel bar weighing 25 pounds, which will be described later, were carried out in a way which permitted an approximate estimation of the foot-pounds of work performed. Naturally the pulse rate and blood pressure could not be taken during the work, but they were taken before and every minute or half minute after work.

Chart 3 represents the type of reaction we obtained in several hundred experiments on twenty normal persons. The delayed rise in systolic blood pressure was obtained after large amounts of work which varied according to the subject's physique and condition of muscular training.

EXPERIMENTS ON PATIENTS WITH CARDIAC INSUFFICIENCY USING THE ERGOMETER

Ten experiments were carried out on two patients who rode the bicycle ergometer for periods of two and one-half minutes with successively increasing loads. Seven experiments were made with the same patients turning the bicycle pedals by hand instead of by the feet. This was done to see if approximately the same amount of work would be followed by a delayed rise in systolic pressure, whether performed by the legs or the arms.

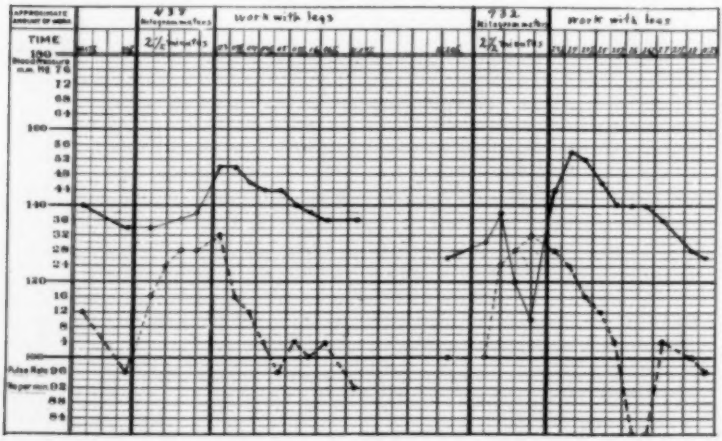

Chart 4.—Circulatory reactions in patient C. G. suffering from cardiac insufficiency to increasing amounts of work performed with the legs on the bicycle ergometer.

Charts 4, 5, and 6 show a typical group of experiments on one of these patients, suffering from mitral regurgitation and cardiac insufficiency. The blood pressure could not of course be measured during the arm work. It will be noticed that 732 kilogrammeters performed with the legs is followed by a marked delayed rise, and 729 kilogrammeters performed with the arms shows an equally marked delay.

The subjects of these experiments both had badly damaged hearts, and histories of two or more attacks of cardiac insufficiency extending over several years.

These experiments present several striking features and some marked contrasts to the experiments on normal persons. The amounts of work necessary to produce the delayed rise in systolic blood pressure were far less than in the normal subjects. Again the pressure *during* work, instead of rising decidedly as in normal subjects, rose but slightly or fell below the pre-exercise level.

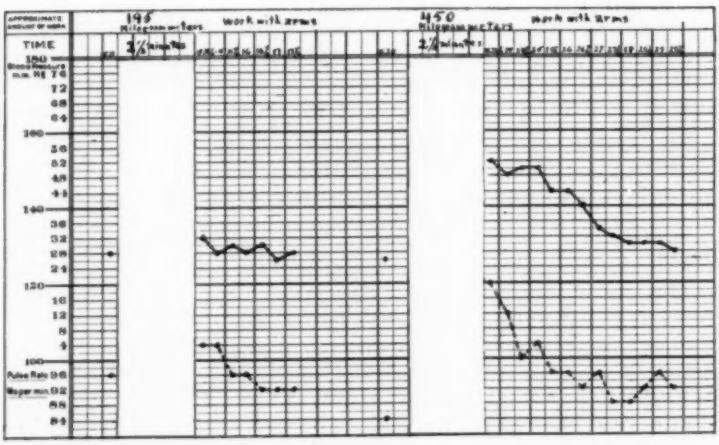

Chart 5.—A continuation of the experiments pictured in Chart 4 on the same patient a few minutes later, the work being performed on the bicycle ergometer with the arms instead of the legs. The white perpendicular spaces represent the work periods in each experiment during which blood pressure and pulse rate could not be measured.

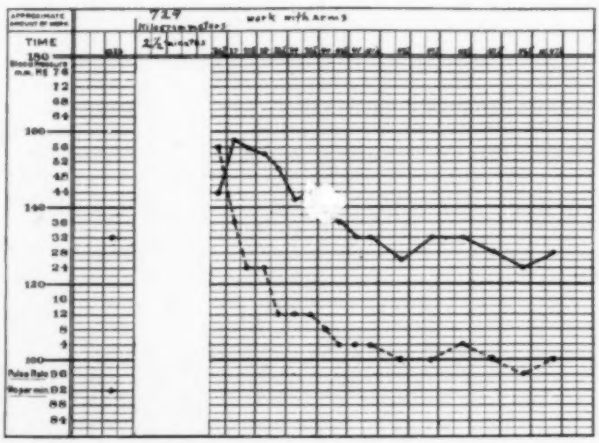

Chart 6.—See legend of Chart 5.

EXPERIMENTS ON PATIENTS WITH CARDIAC INSUFFICIENCY USING DUMB-BELL WORK

Several hundred experiments were carried out on thirty different patients. The pulse rate and blood pressure could not be taken during the performance of the dumb-bell work, but were measured every thirty or sixty seconds after work.

The following examples are selected because they represent the different types of reactions following work.

R. S., a delicate girl aged 23, with a history of chorea and tonsillitis followed by endocarditis. This resulted in a mitral stenosis and regurgitation and, five months previous to the test below described, cardiac decompensation from which she slowly recovered under rest and digitalis.

Time	Pulse Rate	Systolic Blood Pressure
10:05	92	108
10:08	96	104
	200 foot-pounds in 30 seconds (5 lb. bell pushed 20 times)	
10:10	114	122
10:10½	108	120
10:11½	92	106
10:16	90	106
	400 foot-pounds in 30 seconds (10 lb. bell pushed 20 times)	
10:18	120	110
10:18½	108	110
10:19½	98	106
10:30	96	110
	480 foot-pounds in 32 seconds (10 lb. bell pushed 24 times)	
10:31	120	114
10:32	102 Delayed rise	122
10:33	90	110
10:34	90	110

C. G., a man aged 31, with a history of four attacks of rheumatic fever, and symptoms of cardiac involvement for four years. June 8, 1915, he was recovering from a six months' attack of acute articular rheumatism. His heart was much enlarged and showed a mitral regurgitation and regular rhythm. He was dyspneic, his legs were edematous, and the edge of the liver could be felt 5 inches below the free border of the ribs in the nipple line. He was put to bed and given digitalis. June 21, the following test was made:

Time	Pulse Rate	Systolic Blood Pressure
10:55	100	136
10:58	88	130
11:00	100	126
	250 foot-pounds in 20 seconds (10 lb. bell flexed 10 times)	
11:02	108	138
:03	108	136
:04	96	132
:05	92	126
:06	90	128
11:22	96	128

	500 foot-pounds in 35 seconds (10 lb. bell flexed 20 times)		
11:23½	106		140
11:24	102		130
11:25	96		136
11:26	92		130
11:28	100		128
11:34½	96		122
	750 foot-pounds in 45 seconds (10 lb. bell flexed 30 times)		
11:37	114		146
11:38	102		136
11:39	102		136
11:42	96		136
11:44	100		122
	1,000 foot-pounds in 40 seconds (15 lb. bell flexed 27 times)		
11:47	126		136
11:48	114	Delayed rise	142
11:49	108		138
11:50	108		134
11:51	96		138
11:52	96		124

These show the ordinary types of reaction to increasing work.

The same patient several months later showed a type of reaction occasionally encountered.

Time	Pulse Rate		Systolic Blood Pressure
10:05	92		124
	462 foot-pounds in 35 seconds (15 lb. bell flexed 15 times)		
10:07	102		140
10:07½			134
10:08	100		134
10:15	92		126
	750 foot-pounds in 35 seconds (20 lb. bell flexed 15 times)		
10:17	108		140
10:17½			136
10:18	84		126
10:20	88		132
	1,000 foot-pounds in 45 seconds (20 lb. bell flexed 20 times		
10:22	108		134
10:22½	96		130
10:23			128
10:23½	90		128
10:29	92		122
	1,250 foot-pounds in 60 seconds (20 lb. bell flexed 25 times)		
10:31	108		126
10:31½	102	Delayed rise?	128
10:32	90		126
10:39	92		126

1,500 foot-pounds in 60 seconds
(20 lb. bell flexed 30 times)

10:43	114		124
10:43½		Delayed	126
10:44	92	rise	124
10:44½	90		128
10:45	84		120
10:46	84		124
10:47	84		122

The blood pressure reactions to work became less and less marked as the work increased, although the pulse became more and more rapid. Finally in the fourth experiment we got apparently a slight delayed rise in systolic pressure, and, when the work was still more increased (fifth experiment) the pressure immediately after work was lower than it was before, although the pulse-rate had risen to 114.

One more example of the last type may be given.

D. C., aged 23, suffering from disease of all the valves except the pulmonary, and cardiac insufficiency, died Jan. 1, 1915. December 9 he showed the following:

Time	Pulse Rate		Systolic Blood Pressure
12:25	84		100
	150 foot-pounds in 20 seconds		
12:26	108		102
:27	96		102
:28	90		102
:30	80		100
12:40	84		98
	200 foot-pounds in 20 seconds		
12:41	104	Delayed	100
:42	96	rise	108
:43	88		106
:48	90		102
1:05	84		106
	350 foot-pounds in 25 seconds		
1:06	108		98
:07	102	Delayed	106
:08	96	rise	110
:09	90		110
:13	90		100

EXPERIMENTS DEMONSTRATING THAT THE AMOUNT OF WORK NECESSARY TO PRODUCE A DELAYED RISE IN SYSTOLIC BLOOD PRESSURE IS THE SAME WHATEVER GROUP OF MUSCLES IS EMPLOYED

This is the first time as far as we can ascertain that this law of circulatory physiology has been demonstrated. Proof of the invariability of this phenomenon was afforded, as previously stated, by three experiments on two patients with cardiac insufficiency, using the ergometer, and also by many other clinical experiments. A few of the latter will be given for this law plays an important part in establishing the validity of our test of the heart's functional capacity.

The patient on whom the following experiments were performed was aged 58 years, had a normal heart and suffered from occasional attacks of moderate hypertension. On each of the five days preceding the experiments described below this patient had been able to do between 1,500 and 1,800 foot-pounds of work before delayed rises were produced.

Time	Pulse Rate		Systolic Blood Pressure
10:45	96		146
1,500 foot-pounds (approximate) in 35 seconds (Work performed with right arm by swinging 20 lb. bell 8 times)			
10:47	108		164
:48	100		160
:49	96		152
:50	92		148
1,800 foot-pounds (approximate) in 40 seconds (Work performed with right arm by swinging 20 lb. bell 10 times)			
11:17	114		154
:18	96	Delayed rise	158
:19	90		156
:20	90		154
:24	84		140
1,800 foot-pounds (approximate) in 40 seconds (Work performed with left arm by swinging 20 lb. bell 10 times)			
11:26	120		156
:27	96	Delayed rise	170
:28	96		156
:29	90		150
:30	90		148
:32	84		140
11:40	9		140
11:45	92		140
1,800 foot-pounds (approximate) in 40 seconds (Work performed with both arms by swinging two 10 lb. bells 10 times)			
11:47	108		154
:48	96	Delayed	164
:49	90	rise	150
:50	90		150
:51	84		142
:52	80		138
11:53	84		136

It will be seen that it makes no difference whether one or both arms are used to do the work, as far as concerns the production of the delayed rise.

E. B., a patient aged 40 years suffering from mitral regurgitation and stenosis and moderate cardiac insufficiency showed the following results:

Time	Pulse Rate	Systolic Blood Pressure
11:28	96	120
400 foot-pounds (12 lb. bell extended 20 times)		
11:29	120	128
:29½	112	126
:30	108	120
:30½	108	116
:31½	104	116
:33	100	116

500 foot-pounds (12 lb. bell extended 25 times)

11:34	124		120
:34½	120	Delayed rise	126
:35	116		122
:35½	104		120
36½	108		116
:50	104		114

396 foot-pounds (12 lb. bell flexed 18 times)

11:51	136	138
:51½	112	130
:52	104	128
:52½	108	122
:53	100	122
:58	104	116

440 foot-pounds (12 lb. bell flexed 20 times)

11:59	140		122
:59½		Delayed rise	134
12:00	108		130
:00½	108		122
:01	108		122
:02	104		120

Five hundred foot-pounds of extensor work and 440 foot-pounds of flexor work produced a delayed rise of blood pressure.

As a general rule to which the above experiment is an exception a patient with mitral disease is able to do more flexor work with the arms than extensor work, before a delayed rise is produced. Extensor work apparently produces an obstacle to the pulmonary circulation because it tends to immobilize the thorax, while flexor work does not do so. Graüpner first called attention to this.

SUMMARY

Our work may be summarized as follows:

Experiments on Three Normal Persons with Ergometer.—During increased amounts of work there was a rise of the systolic blood pressure and an increase of the pulse rate which became very marked with heavy work. *After* heavy work the delayed rise in systolic blood pressure was noted.

Experiments on Normal People with Dumb-Bell Work.—Several hundred experiments on twenty normal people showed the delayed rise in systolic pressure *after* heavy work.

Experiments on Two Patients with Cardiac Insufficiency Using the Ergometer.—Ten experiments showed a marked contrast in the course of the blood pressure during work as compared with that in normal persons. In these patients the pressure rose but slightly and as the work increased frequently dropped below the original level. The pulse rate was always quickened. The delayed rise in systolic blood pressure occurred after much smaller amounts of work than in normal persons. Approximately the same amounts of work were followed by a delayed rise whether performed by the arms or legs.

Experiments on Patients with Cardiac Insufficiency Using Dumb-Bell Work.—Several hundred experiments were carried out on thirty patients. The delayed rise in systolic blood pressure was noted in all these patients after comparatively small amounts of work. In patients with marked cardiac insufficiency the pressure immediately after work was occasionally lower than the original level.

THE CIRCULATORY PHYSIOLOGY OF EXERCISE

Certain facts about the circulatory physiology of exercise seem to be fairly well established, and we shall summarize them briefly.[2] The carbon dioxid content of the blood is increased by muscular work and this stimulates the nervous centers controlling the suprarenal glands. An increase in the adrenin content of the blood is thereby produced, which causes a constriction of vessels in the splanchnic area and a resulting rise in blood pressure. The quickened heart rate accompanying muscular work causes an increase in the quantity of blood discharged by the heart per minute and this also contributes to the rise in blood pressure. Shortly after exercise stops, the carbon dioxid content of the blood falls below normal, the activity of the suprenal glands decreases and the splanchnic vessels relax.

Nicolai and Zuntz[3] have made some important observations on the hearts of a series of normal persons during work on a stationary ergometer by means of the Roentgen ray. If their experiments are confirmed they will have a very direct bearing on the explanation of the delayed rise in systolic blood pressure and its relation to the testing of the heart's functional capacity. They showed that during moderately heavy work the heart increases slightly in size and a few seconds after work suddenly becomes smaller than normal. The increase during work they attribute to the greater quantity of blood pumped into the heart by the muscular and respiratory activity incident to work. They also offered proof that the heart completely empties itself at each systole of this much increased content, whereas the heart of a resting person expels only about one-half of its contents at each systole. The increase in size during work is not to be regarded as a sign of insufficiency because the heart expels its entire content at each systole. Only if a greater quantity of blood than normal remains in the heart after systole does an insufficiency exist. The rapid diminution in size of the heart immediately after work is attributed to the sudden decrease in the quantity of blood pumped into the heart resulting from the stopping of muscular activity.

2. Cannon: Am. Jour. Physiol., 1914, xxxiii, 356. Von Anrep: Eng. Jour. Physiol., 1913, xlv, 318. Hooker: Am. Jour. Physiol., 1911, xxviii, 235. Schneider and Havens: Am. Jour. Physiol., 1915, xxxvi, 239.

3. Nicolai and Zuntz: Berl. klin. Wchnschr., May 4, 1914, p. 821.

Our own experiments and the facts of circulatory physiology already adduced together with the observations just quoted, give us some insight as to the cause of the delayed rise in systolic blood pressure following work. It may be stated as follows:

In normal people during heavy work the systolic pressure mounts rapidly and the left ventricle finds it more and more difficult to expel its contents against this increasing resistance. At a certain height of aortic pressure the ventricle probably does not empty itself completely and a steadily increasing volume of blood remains in the heart after each systole. In other words, an insufficiency exists. At this moment the Roentgen ray would possibly show a heart decidedly increased in size instead of slightly increased, as found by Nicolai and Zuntz during moderate work. If the work stops the vessels of the splanchnic area begin to relax and the blood pressure falls. Now the heart works more efficiently against the lowered aortic pressure and expels a larger quantity of the increased residual blood at each stroke, until finally it empties itself completely with each systole. The increased quantity of blood which the recovering heart thus throws into the aorta more than compensates for the pressure-lowering effect of the dilating splanchnic vessels and the pressure rises briefly, thereby producing the delayed rise in blood pressure.

The different course of the curve of the blood pressure *during* the work period in patients with cardiac insufficiently implies a difference in circulatory mechanics in these patients as compared with normal persons. This curve showed a slight rise and often a fall with increasing work. The curve *after* work was the same as in normal individuals, except that much smaller amounts of work produced the delayed rise.

The splanchnic vessels in these persons presumably contract during work in the same way as in a normal person. The failure of the blood pressure to rise decidedly during work shows that the heart must propel, if anything, less blood per minute into the aorta than when at rest, even though the rate is much increased; otherwise with a narrowed stream-bed and the same volume discharged per minute the pressure would rise.

Nicolai and Zuntz claim that during work much greater quantities of blood flow into the heart and are ejected at each systole. In our experiments the heart could not have expelled these increased quantities of blood or, as we have already said, the pressure would have risen. Therefore, the blood must have accumulated in the heart and produced a dilatation or insufficiency. The narrowing of the stream-bed caused by the splanchnic constriction incident to work must also play a part in producing this insufficiency.

When the work stops, the stream-bed resumes its normal proportion, possibly more slowly than in a healthy person, the heart acts more efficiently, and expels the increased residual blood, which is sufficient to produce a rise in blood pressure. If the heart is much dilated it probably requires a short time to reach its maximum efficiency and expel its increased content and we have a slowly mounting blood pressure. In other words, our "delayed rise in systolic pressure."

Therefore, if we accept this tentative explanation of the circulatory physiology of exercise, a delayed rise in systolic pressure after work in a normal person or in one with cardiac insufficiency would mean that the preceding work had either made the heart temporarily insufficient or had increased an already existing insufficiency.

Our *clinical experiments* demonstrate conclusively, we believe, that in the pulse rate and blood pressure reactions to graduated work we possess a valid test of the heart's functional capacity. If the systolic blood pressure reaches its greatest height not immediately after work but from 30 to 120 seconds later, or if the pressure immediately after work is lower than the original level, that work, whatever its amount, has overtaxed the heart's functional capacity, and may be taken as an accurate measure of the heart's efficiency.[4]

Graüpner[5] in 1906 carried out a large number of experiments on normal people and persons suffering from cardiac insufficiency, using a Zuntz ergometer and employing the method of frequent blood pressure readings before, during and after work. He reached the following conclusions:

"1. Moderate work in powerful persons causes no change in the systolic blood pressure after work.

"2. An increase in work causes a rise in the systolic blood pressure immediately after work and this returns quickly to normal. Repetition of the work causes the blood pressure to rise less high and to return more quickly to normal.

"3. If the work is still more increased we find directly after work a *sinking* of the blood pressure. Yet the blood pressure then rises quickly above normal and then falls back to normal. This primary fall of the blood pressure and secondary rise above normal is characteristic of 'functional insufficiency' of the heart.

"4. If the blood pressure after work is lower than normal and then slowly returns to normal, but does not rise *above normal*, a primary

4. The determination of delayed rises in patients suffering from auricular fibrillation is difficult and inexact. We have taken the first well-marked beat heard at each reading as a guide. Here the increase in heart-rate is an important aid in deciding if the preceding work has overtaxed the heart.

5. Ztschr. f. exper. Path. u. Therap., 1906, iii, 113; Deutsch. med. Wchnschr., 1906, No. 26.

myocardial weakness exists. This reaction is characteristic of pathological insufficiency."

By the term "normal pressure" Graüpner presumably meant the pressure when it had reached a constant level just previous to the work. Apparently he did not take the pressure before each experiment. The amounts of work performed in his experiments were about the same as in ours. His blood pressure readings were all made by palpation and he generally made three or four in the course of thirty or forty seconds without letting the air out of the cuff.

We were able to corroborate his first conclusion and the first half of his second conclusion. His fourth conclusion we found true in a very small number of patients with cardiac insufficiency. His remaining conclusions, which constitute the essential features of his test, we were unable to confirm.

Graüpner's failure to measure the pressure before each experiment explains to a certain extent the divergence of our results, for the pressure may be as much as 20 mm. of mercury lower before the last experiment than before the first. Also the error inherent in the palpatory method of taking blood pressure especially if the arm be compressed for 30 seconds is considerable and may explain some of our differences.

METHOD OF PERFORMING OUR TEST OF THE HEART'S FUNCTIONAL CAPACITY

The apparatus used consists of pairs of 5, 10, 15 and 20 pound dumb-bells, and a steel bar about 40 inches long weighing 25 pounds. Two types of movements are done with the bells.[6] In the first a pair of dumb-bells is held at the shoulders, one in each hand, and then pushed alternately above the head and toward the median line until the arms are fully extended. As one bell moves up fairly rapidly the other bell returns to the shoulder, the two moving in a sort of see-saw rhythm. In the other movement a bell is held in each hand, the arms hanging by the side of and close to the body, and then each forearm is alternately flexed, raising the bell to the shoulder. The patient stands or sits according to his condition. But one movement is performed with the steel bar. It is picked up from the floor with both hands, raised first to a level with the shoulders, then pushed above the head until the arms are fully extended and then quickly lowered to the floor again with a single rapid motion.

It is possible to calculate approximately the number of foot-pounds of work performed in each of these movements. There is a certain amount of work, however, which we cannot estimate in foot-pounds.

6. These movements were first described by Dr. Jacob Teschner of New York.

When a patient stands with a pair of dumb-bells at his shoulders without moving them, work is done as shown by his circulatory reactions, but we cannot estimate it in foot-pounds. This unknown factor can be ignored, however, for our purpose.

More adults average 2 feet as the distance through which a bell is pushed from the shoulder to full extension of the arm. In the flexion movement, the distance through which the bell is carried from the side of the body to the shoulder averages from 2 feet to 2 feet 6 inches. Now if a 5-pound bell is pushed through 2 feet, 10 foot-pounds of work are done. If the total number of pushes are twenty, 200 foot pounds are done. For the sake of comparison, the time it takes a patient to do any quantity of work should be noted.

If the patient whose heart is to be tested has but recently recovered from an attack of cardiac insufficiency, it is well to start with a pair of 5-pound bells, the patient sitting on a stool. Two hundred foot-pounds of work are then given either by flexing or extending the bells. The pulse rate and blood pressure are taken every thirty seconds according to the examples given on a preceding page. After the pressure and pulse have returned to the original, 300 or 400 foot-pounds are done in the same way. The work is increased with each experiment until we reach a delayed rise in blood pressure. *The experiment which has caused a delayed rise should always be repeated after a few minutes' rest, with a slightly increased amount of work, for the purpose of confirmation.* When once the amount of work which will produce a distinct delayed rise in blood pressure is ascertained, it is quite remarkable how little the results vary on a repetition of the experiment with the same or increased work. Yet if our test is valid this should be so.

The following examples illustrate this point:

This patient was 64 years old and suffered from aortic regurgitation and cardiac insufficiency.

Time	Pulse Rate	Systolic Blood Pressure
3:45	80	132
160 foot-pounds (10 lb. bell extended 8 times)		
3:46	88	138
:46½	80	134
:47	80	134
:47½	80	132
:48	80	134
:49	80	134
3:55	80	130
200 foot-pounds (10 lb. bell extended 10 times)		
3:56	88	142
:56½	84 Delayed rise	146
:57	80	142
:57½	76	122
:58	76	136
:59	80	132
4:03	80	130

240 foot-pounds (10 lb. bell extended 12 times)			
4:04	88		136
:04½	84		142
:05	84	Delayed	138
:05½	80	rise	144
:06	80		144
:06⅓	76		138
:07	80		144
:08	76		134
:09	76		128
4:13	76		130

As a general rule a patient's cardiac capacity will vary but slightly from day to day. If he improves in general condition his cardiac capacity increases, and if he retrogrades it decreases. Lack of sleep or transient infections have very prompt and decided effects on the cardiac capacity, particularly in persons who already have damaged hearts.

The following examples illustrate this point:

July 7 a patient with a mitral lesion and cardiac insufficiency showed the following reaction (he had been able to do between 600 and 900 foot-pounds each day but not more, during the three weeks previous to this date):

Time	Pulse Rate	Systolic Blood Pressure
11:15	92	120
	750 foot-pounds in 40 seconds (15 lb. bell, extended 25 times)	
11:16	116	128
:17	104	130
:18	96	128
:19	96	124
:20	96	124
:22	100	124
:23	92	120
	900 foot-pounds in 40 seconds (15 lb. bell flexed 25 times)	
11:26	116	138
:27	108	130
:28	96	126
:29	96	116
:30	96	122

On the afternoon of July 7 the patient became very angry, so much so that he "trembled for three hours afterward." That night he slept but a few hours. On July 8 he showed these reactions:

Time	Pulse Rate	Systolic Blood Pressure
11:37	92	124
	375 foot-pounds in 20 seconds (15 lb. bell flexed 10 times)	
11:38	104	136
:39	96	136
:40	92	132
:41	90	126
:42	98	130
:43	96	128
:44	92	126
:45	92	122
:46	96	120

560 foot-pounds in 25 seconds
(15 lb. bell flexed 15 times)

11:47	108		120
:48	104		134
:49	104	Delayed rise	134
:50	104		134
:51	100		130
:52	96		124
12:01	96		120

725 foot-pounds in 30 seconds
(15 lb. bell flexed 20 times)

12:03	108		126
:04	104	Delayed	130
:05	96	rise	130
:06	100		132
:07	104		130
:08	96		128
:09	92		124
:10	96		120

July 9 he was again able to do 750 foot-pounds and July 30 he did 1,400 foot-pounds in sixty seconds.

Another patient suffering from renal tuberculosis and a stricture, but with a normal heart, had lost much weight and sleep, being obliged to pass urine every hour.

May 11, 600 foot-pounds of work caused a delayed rise in blood pressure. His stricture was then relieved, he began to sleep normally, his appetite returned and he was able to take daily walks. May 21, 1,500 foot-pounds of work were performed before a delayed reaction ensued.

Rarely we find that our results are not unvarying. We have records of one man with a presumably normal heart who showed a very distinct delayed rise with 640 foot-pounds of work performed in twenty-two seconds, and thirty minutes later did not show a delayed rise until about 1,300 foot-pounds of work in twenty-five seconds had been done.

The Testing of Patients Whose Cardiac Capacity Exceeds an Ability to Perform 1,000 Foot-Pounds of Work in 60-90 Seconds.—People with normal hearts, or patients with well compensated heart lesions, afford a more difficult problem in mechanics when their hearts are functionally tested. These people are able to flex or extend heavy dumb-bells until their arm muscles are exhausted and yet the heart muscle will show no exhaustion. That is, no delayed rise in the systolic blood pressure is obtained. Here it is necessary to use more powerful muscles, capable of doing much greater amounts of work, in order to tire the heart. We use in these people the 25-pound steel bar which is lifted from the floor to the shoulder and above the head until the arms are fully extended. Then it is lowered quickly to the floor and raised again above the head. An adult will raise the bar between 6 and 7 feet, performing thus between 150 and 175 foot-pounds with each raising. In addition to the work arising from the bar movement, the raising of the trunk of the body each time from a

stooping to an erect position is equivalent to a certain number of foot pounds. The exact number is very difficult to estimate, but from some comparative experiments we are now carrying out it apparently lies between 40 and 50 per cent. of the body weight. That is, a man who weighs 150 pounds does between 60 and 75 foot-pounds of work each time that he raises his body from a stooping to an erect position.

The testing of these hearts is necessarily at the present time a comparative matter, and we are unable to obtain absolute values, unless we have a bicycle ergometer at our disposal.

One example of these normal cases will be given:

Male, adult, aged 41, weighing 160 pounds, with a normal heart.

Time	Pulse Rate		Systolic Blood Pressure
8:36	68		112
800 foot-pounds (20 lb. bell pushed 20 times)			
8:35½	84		120
:36	72		122
:37	66		120
:38	66		116
:39	66		118
:43	66		110
1,000 foot-pounds (20 lb. bell pushed 25 times)			
8:45	84		124
:45½	72		120
:46	72		112
:47	72		110
:55	66		112
2,400 foot-pounds (approximate) (25 lb. bar lifted 7 feet 10 times)			
8:56½	108		{ 134
:57	84	Delayed?	{ 136
:57½	66		116
:58	66		114
:59	66		112
3,360 foot-pounds (approximate) (25 lb. bar lifted 14 times)			
9:01	114		{ 136
:01½	84	Delayed?	{ 138
:02	72		130
:03	76		126
:04	66		114
4,800 foot-pounds (approximate) (25 lb. bar lifted 20 times)			
9:08	120		{ 136
:08½	90	Marked delay	{ 146
:09	78		136
:10	72		130

SUMMARY

A large number of experiments have been carried out on normal persons and those suffering from cardiac insufficiency to determine the effect of graduated work on the pulse rate and systolic blood pressure. The work was performed by means of a Krogh bicycle ergometer in a few persons and by dumb-bell exercises in the majority of subjects.

It has been demonstrated that a certain form of the curve of systolic blood pressure determined *after* the completion of work is characteristic of an overtaxing of the heart's functional capacity.

A tentative explanation has been given of the circulatory physiology of exercise (work).

A practical test for estimating the heart's functional capacity has been described.

It is a pleasant duty to express our thanks to Dr. Horatio B. Williams of the Department of Physiology of Columbia University for his assistance in supervising the experiments conducted with the bicycle ergometer, and for many valuable suggestions made during the course of the work outlined above. Also we are indebted to Mr. R. McIntosh for much help in the experiments with the ergometer.

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SOME ATTEMPTS TO PRODUCE EXOPHTHALMOS EXPERIMENTALLY*

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In a paper[1] published in 1914 I endeavored, on the basis of a number of clinical and experimental observations, to make a contribution to our knowledge of the pathogenesis of the eye symptoms in exophthalmic goiter. I dwelt in that connection particularly on Landström's explanation of their origin, and, making reference to our present anatomic and clinical information, expressed my doubts as to the possibility of maintaining Landström's theory. The chief points on which I based my remarks were the following:

1. The "Landström muscle," or rather the musculus capsulopalpebralis (Hesser[2]), is so weak and so asymmetrically placed as to be hardly capable of producing alone the pronounced eye symptoms which are not infrequently observed in exophthalmic goiter. Above all, it is difficult to understand how a contraction of that muscle should produce a pronounced shifting forward of its posterior origin (of the region about the equator of the eyeball), and thus of the entire eyeball, and not a shifting back of its anterior origin (septum orbitale in the eyelid), since the former is a point considerably more fixed than the latter. Sattler[3] and Hesser have given grounds in their anatomic investigations for these views and have emphasized their importance.

2. Even when we assume that the smooth muscle in the orbit can shift the bulb in a forward direction, we encounter great difficulties in trying thus to interpret the genesis of the eye symptoms in exophthalmic goiter. For, assuming that the contracted condition of the muscle that would produce them is directly the result of a stimulation of the supplying nerve — the sympathetic — we must not overlook among other things two of the peculiarities of the exophthalmic goiter syndrome. In the first place, the eye symptoms, as I have found, in 10 per cent. of the cases, are rather frequently on one side only; in the second place, the pupillary signs are not a part of the regular exophthalmic goiter symptoms and may, even in extreme exophthalmos of that disease, not be observed at all. The one-sided nature of the eye symptoms is extremely hard to understand, if we accept Moebius' theory that the nature of exophthalmic goiter is chiefly that of an intoxication of the sympathetic nervous system, by poisonous decomposition products disseminated by the general circulation from the thyroid gland. And the absence of pupillary symptoms is in equally great measure incomprehensible if we accept the opposite view of the origin of the sympathetic stimulation, that it is a more direct, mechanical effect of a thyroid enlarged on one or both sides of the nerve. For we must then inquire why

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1. Troell, Abraham: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, xxvii, 418.
2. Hesser: Anatomische Hefte, 1913.
3. Sattler, in Graefe-Saemisch: Handbuch. der gesamten Augenheilkunde. 1911; Ber. ü. d. 37. Versamml. d. Ophth. Gesellsch., Heidelberg, 1911, Wiesbaden, 1912, p. 181.

an effect of such limited compass should exercise no stimulation on those fibers in the cervical sympathetic that run to the smooth muscle of the eyeball (musculus dilatator pupillae), but should affect only those that go to the smooth muscle of the orbit (musculus capsulopalpebralis), since it is well known that an electric stimulation of the cervical sympathetic always produces in man, as well as in related animals, chiefly a dilatation of the pupil, with a widening of the lid-cleft and possibly a bulging out of the eyeball, while conversely, the cutting of the sympathetic cord will produce corresponding paralytic symptoms in both these muscular tracts (contraction of the pupil, narrowing of the lid-cleft, etc.).

Logical as the foregoing reasoning may be, it suffers from the imperfections of our present anatomic and clinical knowledge. Perhaps the future may disclose data that will show this chain of evidence to be not equivalent to a full proof. Possibly the eye symptoms in exophthalmic goiter are produced by toxic influences similar to those we have reason to believe are present in the "system diseases" of the central nervous system, or to those which enable a poison, like amyl nitrite, on being inhaled to affect the vagus fibers that proceed to the heart, but not those that proceed to the digestive tract. Hesser,[4] in a recapitulatory article of recent date, has emphasized the conditions produced by amyl nitrite. He suggests the possibility that the exophthalmic goiter toxin may produce exophthalmos in man by influencing certain nerve elements running to the orbit, in a manner resembling that of amyl nitrite which preferably affects the cardiac vagus fibers.[5] But we must point out that neither this analogy nor the analogy with the behavior in nervous "system diseases" for the present is of great value in determining to what extent the absence of pupillary symptoms in exophthalmic goiter militates against Landström's theory of eye symptoms. For, applied to the phenomena in exophthalmic goiter, such an analogy would imply the possibility that the toxins of the thyroid gland, disseminated by the circulation, should be able for a protracted period, to influence *only* on *one* side, *some* of the sympathetic fibers, or of the sympathetic ganglion cells (those belonging to one musculus capsulopalpebralis). Such a hypothesis, in view of our present state of medical knowledge, constitutes a quite peculiar and unsatisfactory complication of the problem.

If one accepts my reasoning as to the significance of the regular occurrence of pupillary symptoms on electric stimulation of the sympathetic, but their absence in typical exophthalmic goiter, one is confronted with a new question: May not valuable data on the genesis of exophthalmos be obtained *from attempts to produce exophthalmos experimentally, without the mediation of the cervical sympathetic?*

It would seem possible to make an attempt to produce exophthalmos by the use of toxic materials, in some cases without any preparatory measures; in others, after having removed the superior cervical sympathetic ganglion *on one side*. If in the latter case, it should be found that exophthalmos failed to appear on the side on which the interruption had been made in the sympathetic, this would be proof

4. Hesser: Hygiea, 1914, lxxvi, 561.

5. Unfortunately he gives no citation of authorities, a circumstance all the more to be deplored since it is characteristic of his entire paper, which otherwise is illuminating. I have, therefore, not been able to determine whether in the investigations under consideration any reliable observation of the fact could be made, that the vagus fibers of the digestive tract remained unaffected.

that the cooperation of the sympathetic is necessary for the production of such exophthalmos; such an outcome of the experiment would thus lend a certain support to Landström's theory. But the opposite would be the case if it should be as easy to produce exophthalmos in an individual whose sympathetic ganglion had been removed so long ago that the nerve fibers situated distally to it—the postganglionic fibers — should have degenerated.

The chief difficulty about the procedure mentioned above is the well-known great difficulty in producing exophthalmic goiter and exophthalmic goiter exophthalmos experimentally. Souppalt probably was the first (1897) to undertake experiments in this direction. He has had many successors, but a study of the literature on the subject gives one the decided impression that the experiments thus far made on animals have only in exceptional cases given rise to an unmistakable protrusio bulbi, no matter what procedure has been followed. The results have been very uncertain, both in cases in which injection of thyroid juice has been resorted to, and in cases of transfer of normal thyroids, goiters, exophthalmic goiters, thymus, etc.[6]

I have, therefore, believed that I should be more likely to obtain results if I should try first and foremost other toxins than those of the thyroid gland and the like in producing exophthalmos. One such, beta-tetrahydronaphthylamin, first used by Stern,[7] has long been known as having a direct affinity with the sympathetic nervous system, and as giving, on subcutaneous injection into animals, symptoms of stimulation from the muscles innervated by the sympathetic nervous system. In cats it produces, among other things, dilatation of the pupil and protrusion of the bulb (Elliot[8]). It would, therefore, be particularly applicable in the investigations I have in mind. But the drug has the disadvantage of being very difficult to obtain commercially at this time. This is not true to so high a degree of another chemical substance, paraphenylenediamin (which Hesser mentions casually in his latest paper). Just how we are to regard the effect of paraphenylenediamin is not known. Probably it does not work directly through the nervous system. Other drugs having a sympathicotonic effect are known, as epinephrin and cocain. Yet their availability for

6. An historical résumé of these experimental investigations is found in Klose (Ergebn. d. inn. Med. u. Kinderheilk. v. Kraus u. a., 1913, x, 167). Of later investigators who claim to have succeeded in producing exophthalmos in animals, there may be mentioned Baruch (Centralbl. f. Chir., 1911, xxxviii, 1185; ibid., 1912, xxxix, 316) and Bircher (Centralbl. f. Chir., 1912, xxxix, 138). See also Biedl (Innere Sekretion, 1913, i, 212) and Kempner (Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1914, xviii, 347).

7. Stern: Virchows Arch. f. Path. Anat., 1889, cxv, 14.

8. Elliot: Jour. Physiol., 1912, xliv, 374.

our present purpose may be considered negligible. It is, in fact, interesting to note that the subconjunctival injection of two such extremely sympathicotonic substances, in spite of the situation near the surface of the capsulopalpebralis muscle, does not produce a bulging of the eyeball of even 1 millimeter, but may, on the other hand, bring about a striking widening both in the pupil and in the lid-cleft. This tells, in its way, against the probability that exophthalmic goiter exophthalmos may be the effect of a stimulation of the sympathetic (Sattler[9]).

Paraphenylenediamin on subcutaneous injection into the sacral region of dogs and monkeys, by Grunert,[10] Birch-Hirschfeld[11] and others, has been found to produce a symptom group including among other things increased epiphora and mucous secretion, chemosis, injection of conjunctiva, increase in intra-ocular pressure, and exophthalmos; the anatomic cause of the latter is a drenching of the orbital tissue with serous fluid.

I repeated these experiments with paraphenylenediamin hydrochlorid Merck (paradiaminobenzene hydrochlorid) on various kinds of animals, sometimes under entirely normal conditions, sometimes after removing the upper sympathetic neck ganglion. An account of these experiments is given in the accompanying table and additions.

For considerations of space, I have limited myself, with regard to my experiments on dogs, to a short tabular synopsis, as, moreover, the symptoms observed by me after paraphenylenediamin injection coincide in the main with those obtained previously by other investigators.

In addition to the upper sympathetic cervical ganglion, in each case in which that operation was performed, from 2 to 3 cm. of cord under it was also removed.

The operative procedure for removing the ganglion is preferably the following: An oblique transverse incision is made corresponding to the base of the skull, beginning right under the easily felt bulla ossea ossis temporalis, in front of the atlas and the muscles originating from that point. The incision is continued downward toward the median line. Laterally behind the large vessels of the neck, the vagus is easily found. In the dog, the sympathetic fibers run along the neck like a fine nerve laterally behind the vagus and in intimate contact with it, the two nerves being enclosed in one common sheath of connective tissue; in the cat, the sympathetic is easily distinguished from the vagus with naked eye; in the rabbit the fibers often run in two separate bundles on either side of the neck. The ganglion cervicalis superior is in dogs very difficult of access for operative purposes. It lies far up toward the base of the skull, on the musculus longus capitis, medially behind the plexus nodosus nervi vagi. Its size is not inconsiderable, usually at least 3 or 4 millimeters in length. Its color is more decidedly bluish-gray than that of the vagus. It is connected

9. Sattler: München. med. Wchnschr., 1911, lviii, 2307; Deutsch. med. Wchnschr., 1912, p. 93.

10. Grunert: Ber. u. d. 31. Versamml. d. Ophth. Gesellsch., Heidelberg, 1903, p. 208.

11. Birch-Hirschfeld, in Graefe-Saemisch: Handbuch der gesamten Augenheilkunde, ix, Chapter xiii, 100.

Paraphenylenediamin Experiments on Dogs*

Number	Dog's Weight, Kg.	P.D. Dose per Kg. Body Weight, Gm.	Eye Symptoms										Other Local Symptoms		Changes in the General Condition						Postmortem Findings
			Epiphora	Edema in Nictitating Membrane	Edema in Conjunctiva Palpebrarum	Edema in Conj. Oculi.	Hyperemia in Conjunctiva	Pur. Conjunctivitis	Increased Depth of the Anterior Chamber	Increased Intra-Ocular Pressure	Protrusio Bulbi	Increased Salivary Secretion	Swelling in the Submaxillary Region	Unrest	Sluggishness	General Appearance of Being Very Sick	Vomiting	Diarrhea	Convulsions (spasms)	Death	
1	4.2	0.075	+	..	+	+	..	..	..	..	+	+	+	+	+	+	+	..	..	..	Brown pigmentation of lacrimal a. submax. glands. Edema in these glands and in the neck lymph glands. Dog died following day during sympathetic operation.
2	5.0	0.075+ 0.075	..	+	+	..	..	..	..	..	..	..	+	+	+	+	..	..	+	+	Lacrimal glands much brown pigmented.
3	3.125	0.075	+	+	+	+	+	+	..	..	..	..	±	+	+	..	+	+	+	+	Hardly any edema visible in the conjunctivae.
4	5.1	0.1 0.1	..	+	+	..	±	+	..	+	+	..	..	+	+	..	+	..	..	..	.....
			..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	..	+	
5	2.975	0.1	..	+	+	..	..	..	..	..	±	..	..	..	..	..	+	+	+	..	(Decalcifying of the orbits; microscopic examination of orbits and orbit contents)
6	13.15	0.08	..	+	..	+	..	..	..	..	+	..	..	+	+	+	..	..	..	..	.....
7	2.95	0.08	..	+	+	..	..	..	..	..	+	..	..	..	+	+	..	..	+	+	.....
8	6	0.09	+	+	+	..	..	..	+	+	+	..	..	+	..	+	..	..	..	+	Eye symptoms still visible, but less evident. (Microscopic examination of the orbits with contents after decalcifying.)
9	6	0.06	+	+	+	..	..	..	..	+	+	..	+	..	+	..	..	..	..	+	Also the submaxillary region was swollen and edematous. (Orbits decalcified and microscopically examined.)
10	6.56	0.04 0.04	..	+	+	+	+	..	..	..	+	..	..	..	..	+	..	..	..	..	.....
			..	+	±	..	..	..	..	..	±	..	..	..	..	..	..	..	+	+	
11	15.98	0.05	..	..	+	+	..	..	+	..	±	..	..	..	..	+	..	..	..	+	No pigmentation of the submaxillary glands.
12	8.84	0.05	..	..	..	..	..	..	..	..	..	+	..	+	+	..	..	..	..	+	(Orbits, with contents, decalcified, and examined microscopically.)

* The sign ± indicates that the symptom in question was only slightly present.

REMARKS
Two hours previous to this injection, the same dose P.D. had been injected in 2 per cent. boric acid solution. As this did not produce any effect, the injection was repeated, 25 per cent. water solution being used and sterilizing being performed by boiling (for all the following cases, P.D. was used in this manner). The eye symptoms appeared three-fourths hour after injection, and were evidently increasing during the five hours following. Yet protrusio bulbi was not marked until the day after, the conjunctival edema then having disappeared. The latter day, ganglia cerv. sup. were removed.
Two hours previous to the first injection, right sup. cerv. symp. ganglion had been removed. The first injection of 0.42 gm. P.D. only produced some conjunctival edema, particularly in the right eye. Therefore the same dose P.D. was injected once more, 3½ hours later. The edema now following was, after 2½ hours, more pronounced on the right side than on the left; dog died shortly afterward.
The day following the injection, the dog was somewhat more lively. Then the left cerv. sup. symp. ganglion was removed. Dog died shortly after.
One week after the injection, every general and local symptom had disappeared, except some corneal opalescence which had been visible for about four days. Left sup. symp. cerv. ganglion was removed. On the third day after that (when no symptom from the first injection was to be seen any longer), the same dose P.D. (0.56 gm.) was injected. At this time the dog did not develop any eye changes but only general symptoms; death followed soon.
Three and one half hours after the injection the dog was etherized. Cannulas were inserted into the right femoral artery and vein, and the dog was bled to death. The whole vascular system was carefully washed out with 0.1 per cent. salt solution. A cannula was inserted into the thoracic aorta, and 5 per cent. liquor formaldehydi was injected in direction toward the head, thus establishing a good hardening in situ of the orbit contents.
Four days later when all eye symptoms had disappeared and the dog seemed quite well, the left sup. cerv. symp. ganglion was removed. The dog died during the operation (from much pulling on and hurting the vagus—respiration paralysis).
One hour after the injection there was a pronounced bulging of the bulbs which with its staring look and almost complete fixity of the bulbs was very much like exophthalmos in exophthalmic goiter. Only a careful examination revealed the edema of the nict. and conj. membranes. This edema increased very much during the two hours preceding death.
Two days previous to the injection, the left sup. symp. cerv. ganglion had been removed. This caused lessening of left pupil and lid-cleft, and enophthalmos sin. Two hours after the injection the eye symptoms (edema of the nictit. and conjunct. membranes) were more pronounced on the left than on the right eye. Five hours after the injection the eye symptoms were equally present in both eyes; now there was also to be seen a bulging of the bulbs, as well as much fixity of them; the pupils were of medium and equal size.
Two days previous to the injection, the left sup. symp. cerv. ganglion had been removed (which had produced the same paralyzing symptoms as in Case 8). The eye symptoms following the injection developed their maximum 3½ hours after the injection, having been increasing a little slower on the right side than on the left. Left pupil was very narrow all the time, right pupil very wide.
Four days previous to the injection, the same ganglion operation was done as in Cases 8 and 9, and with the same effect. During the first hours following injection, the eye symptoms were more pronounced on the left side. Later on, there was no evident difference between these changes on either side. Yet the symptoms remained longer on the left side than on the right, still a week later there was some conjunctivitis on the left eye. Seventy-one days after the ganglion extirpation, left pupil still was small (and elliptical in vertical direction), slowly reacting; left lid-cleft was just a little narrower than right; enophthalmos sin. was not unquestionable. Another P.D. injection was done. Eye symptoms developed, but more pronounced on the left side than on the right, though not even on the former very strong. Death followed soon.
Ganglion cerv. symp. sup. sin. was removed sixty-four days previous to the injection. Paralyzing effect as in earlier cases (and also purulent conjunctivitis sin.). Two days later the epinephrin test of Loewi was negative on both eyes. Three weeks later the symp. paralyt. symptoms were, on one day, less pronounced than before that time; once the pupil was found elliptical in a vertical direction. Two months later the paral. symptoms (even the enophthalmos) were very evident. The inj. symptoms reached their maximum 6 hours after the injection, equally pronounced on both eyes; death occurred some hours later.
One hundred and eleven days previous to the operation, the left phrenic nerve had been cut (as far down in the neck as possible), whereupon its proximal end had been turned upward and sewed to the distal end of the sympathetic (which also had been cut, close below the superior ganglion). At the necropsy the nerve suture was nicely healed and not to be detected. The dog had all the time showed paralyzing symptoms on the left eye (small pupil, small lid-cleft, pulling forward of the nictit. membrane and enophthalmos; yet the latter had by and by become less pronounced).

below by a number of its branches with the vagus, from which it is difficult to separate them. When the sympathetic cord has entered the thoracic cavity, it forms the ganglion cervicalis inferior and separates from the vagus.

In addition to these experiments on dogs, I have also made injections of paraphenylenediamin on a cat, a rabbit and a guinea-pig. The results obtained were not, as the report below will show, entirely similar to those obtained from dogs.

CAT 13.—Weight 3,390 gm. Nov. 16, 1914, received subcutaneous injection in lumbar region of 0.25 gm. of paraphenylenediamin (0.075 gm. per kilogram body weight). Immediately after this the pupils were small and reacted to light; cat was sluggish and discontented. Two hours after injection, pronounced swelling beneath the lower jaw, considerable conjunctival edema, so that the eyelids could not close; no noticeable exophthalmos; pupils of medium size; considerable general depression. The cat died shortly after. Postmortem examination showed much edema in the lower jaw region, as well as subconjunctivally, but nowhere any brown pigmentation. The orbits with their contents were examined microscopically. (In this case as well as with the other animals on which such examination was made — the rabbit, the guinea-pig, and three dogs — the animal's head was first hardened in liquor formaldehydi, whereupon each orbit was sawn out of its place and decalcified in 5 per cent. solution of nitric acid; celloidin sections of horizontal and sagittal — and in one dog, oblique — meridians were made of the decalcified specimens).

RABBIT 14.—Weight 590 gm. Nov. 14, 1914, the pupils were wide, equally large and reacting to light; 0.013 gm. of paraphenylenediamin were injected subcutaneously (0.075 gm. per kilogram body weight). No effect whatever was observed within one hour; therefore the same dose was again injected. November 16, no perceptible effect; pupils as before; injection made of 0.135 gm. of paraphenylenediamin. Without having previously shown any noteworthy symptom, the animal one and three-fourths hours after last injection was suddenly attacked by clonic general convulsions, which resulted in death in a few minutes. The necropsy revealed nothing of interest.

GUINEA-PIG 13.—Weight 600 gm. Nov. 16, 1914, pupils wide, reacting to light; 0.045 gm. paraphenylenediamin injected subcutaneously. November 17, no perceptible effect; another injection, same dose. November 18, no perceptible effect. November 23, animal still well; killed under ether. Necropsy showed nothing of interest.

From the records of the operations, it is evident that the paraphenylenediamin injection, as far as eye symptoms, particularly exophthalmos, are concerned, gave positive results in the case of the dogs, but a negative result with cat, rabbit and guinea-pig.

The time for the appearance of the symptoms varied, both for the local phenomena and for those of general nature. Usually the dog which had received an injection gave evidences of great unrest, apparently because of pain at the place of injection. Thereupon followed a condition of general dulness. The dog would lie on the floor limp and give the impression of being very sick. In five of the cases occasional vomitings occurred in the next few hours, in three cases diarrhea. Clonic convulsions, especially in the lower jaw, back of neck, and in the extremities, were observed in five animals, usually

continuing until death ensued. In Case 2 there was no typical convulsion, but slight twitches in the extremities, giving the gait a somewhat spastic ataxic appearance. A lowering in blood pressure was observed in Dog 10, the only animal in whose case such a record was made.[12]

Eye symptoms failed entirely to appear for several hours in one case (Case 12). The injection was made in the afternoon. I had no opportunity to observe the dog for more than three hours after that, and in the following night he died. In all the other cases, paraphenylenediamin injection in dogs was followed by more or less pronounced changes in the region of the eyes (and in same cases also around the submaxillary gland). These symptoms appeared within from one-half to two hours after injection, reached a maximum during the following four or five hours, and in case of the animal surviving, had usually disappeared in a week. In one dog (Dog 7) within one hour after injection a bulging of the eyeballs was observed, which, with its characteristic staring expression and the almost immovable fixity of the eyeballs, reminded one of exophthalmic goiter exophthalmos; on closer examination there was found an incipient edema in the nictitating and conjunctival membranes which increased decidedly later, and thus made this case rather like the others. The invariable characteristic in these eye symptoms was an edema which, in almost all cases, was first observed in the membrana nictitans and the lower conjunctiva palpebrarum and then spread to the conjunctival membrane in its entirety, constantly increasing in quantity. In three cases, the eye syndrome was limited to an edema in the nictitating and conjunctival membranes with no (Case 2) or very slight (Case 10—second injection—and Case 11) protrusio bulborum. In the other cases there developed, besides the externally recognizable edematous swelling, sooner or later an unmistakable bulging out of the eyeballs, which in a few exceptional cases persisted even after death. In two cases (Cases 8 and 11) the depth of the anterior chamber was increased; in three (Cases 4, 8 and 9) there was found a noteworthy increase in intra-ocular pressure. Often the edematous swelling at

12. This experiment was carried out at the second paraphenylenediamin injection as follows: The dog was put under ether. A cannula connected with a mercury manometer and with an ordinary registering kymograph was inserted into one of the carotids, whereupon 0.3 gm. paraphenylenediamin was injected subcutaneously. Before injection, the blood pressure was about 100-110. Ten minutes later it stood at 80; twenty-five minutes later, when the dog had been permitted to come out of the narcosis in part and no longer lay limp, the figure rose to 110-120 for a few minutes. He was then put into a deeper sleep. After ten minutes, 70 was registered, after which the figure kept at about 80. An hour after injection, the experiment was stopped because of coagulation of the blood in the cannula and supply tube.

the maximum of the changes was so pronounced that the eyelids could not be closed. It was not possible to determine any other anatomic basis for the symptoms than an edematous accumulation in the tissues; in none of the species could any venous thrombosis be histologically demonstrated.

Size and reaction power of the pupils were recorded, but were often difficult to determine precisely, because of the presence of chemosis. Only in one of the animals did they show a change that could be attributed to the injection. In this case (Case 8) the left pupil was contracted before the injection because of operative paralysis of the sympathetic, but five minutes after injection both were of equal and medium size. The reason for this may, in my opinion, be the alteration in the conditions of the circulation resulting from the injection, as is observed, for instance, in glaucoma, in which condition, together with an increased intra-ocular pressure, there is also a widening of the pupils, no longer reacting to light (and where there is no suggestion of interpreting these symptoms as the result of sympathetic stimulation).

Particular mention must be made of the experiments in which one of the upper sympathetic cervical ganglia had been removed before injection. The effect of this operation per se — before any injection was made — was of course a paralysis of the muscles within the orbit supplied by the sympathetic bundles; lid-cleft and pupil became smaller, the nictitating membrane was pulled forward toward the pupil,[13] and the eyeball appeared to recede into its socket. The extent of each of these symptoms varied somewhat. The most constant factors were the decrease in the size of pupil and lid-cleft; they were never lacking for a certain period after operation. Less unquestionable were, sometimes, the forward tendency of the nictitating membrane, and enophthalmos. After a few weeks, or at most months, the decrease in the size of the pupil was, as a rule, the only remaining symptom that was completely evident; an adjustment to the normal appeared to have set in, both with regard to the width of the lid-cleft and, above all, the position of the bulb.

Now, what was the nature of the eye symptoms after paraphenylenediamin injection in those animals in which a paralysis of the sympathetic on one side had been practiced? This was noted in seven of the experiments with the following results:

1. The eye symptoms were never less pronounced on the side of the paralyzed sympathetic than in the other eye.

13. This symptom was distinctly observable, but not in a pronounced degree, in Cases 10 and 11; more pronounced in Case 12. In another connection I shall probably dwell more exhaustively on the details of these paralytic symptoms.

2. In two cases (Case 2 and Case 10, second injection) in which the animals lived only a few hours after the injection of paraphenylenediamin, the eye changes were somewhat more pronounced on the side on which operation was performed than on that not operated on. The upper cervical ganglion had been removed two hours and seventy-one days, respectively, before the injection.

3. In three cases (Cases 8, 9 and 10, first injection) the eye symptoms, which included protrusio bulborum during the hours immediately following injection, were most pronounced on the side on which operation was performed, but did not present any unquestionable dissimilarity between right and left eye at the time of maximum effect. In these cases the injection had been made from two to four days after removal of the sympathetic ganglion.

4. In two cases (Cases 11 and 12) which received injections sixty-four and 111 days, respectively, after production of the sympathetic paralysis, and which resulted in death within twelve hours after injection, no dissimilarities whatever were observed in the eye symptoms of both sides. Yet the symptoms were in the former case very faint, and in the other not quite beyond doubt.

A summary of these data could yield this result: In the first place, *the eye symptoms produced by paraphenylenediamin, which usually include protrusio bulborum, may be brought about without the intermediation of the cervical sympathetic.* No evidence has been offered for supposing that the cooperation of the sympathetic is necessary for producing the eye symptoms, but it has been shown experimentally that the latter is possible even when the injection is made so long after the removal of the upper sympathetic cervical ganglion that the nerve units situated distally to it may be considered to have already degenerated. In the second place, these paraphenylenediamin experiments show that the final effect of the injection, if it is undertaken after one of the cervical sympathetics has been cut out, will still be produced and will be equally pronounced in both eyes, but it develops more slowly and comes out later in the eye on the side on which operation has been performed. The most plausible explanation of this is probably to be found in the fact that the fibers of the cervical sympathetic that go to the vasoconstrictors predominate over those that supply the vasodilators.[14] The bringing about of a sympathetic paralysis has resulted, therefore, among other things, in a dilatation of the corresponding carotid branches on the operated side, which may have involved the opportunity for a more rapid appearance of

14. See, for example, Frank's "Hämodynamische Operationen" in Tigerstedt's Handbuch der physiologischen Methodik, 1911, ii, Part 4, p. 364. Meltzer, S. J., and Meltzer, C.: Am. Jour. Physiol., 1903, ix, 147.

the edema, essentially limited to the contents of the orbit which is the chief anatomic effect of a paraphenylenediamin injection.

In connection with the investigations described above, I might refer briefly to other experiments which I made with the purpose of producing exophthalmos. Their results were entirely negative, as far as eye symptoms are concerned, but they may nevertheless be of interest. They were based on the assumption that a chronic stimulation of the cervical sympathetic may produce a bulging of the eyeball. MacCallum and Cornell[15] have proved on dogs that a temporary protrusion may be brought about by the application of an electric current to the cervical sympathetic; they were able to make graphic records of the amount of bulging. I tried without success to repeat the experiments on dogs (three cases), cats (three cases) and rabbits (one case); notwithstanding the use of a very strong interrupted current, I obtained hardly any other striking phenomenon than a maximum dilatation of pupil; no unmistakable exophthalmos was produced, though perhaps there was bulging of 1 or 2 millimeters in the case of one cat. I once had occasion to observe a neck operation on a patient in which the corresponding effect was to be noted; electric sympathetic stimulation brought about dilatation of the pupil, but no visible exophthalmos. And in the paper of MacCallum and Cornell,[15] the same observation is mentioned by them from two patients. Jonnesco[16] is the only one whom I have known to announce a positive result of such experiments; on applying a strong electric current to the sympathetic, he noted the appearance of exophthalmos in man.

In order to bring about a chronic sympathetic stimulation, I have made use of the same principle as that successfully employed by Timme[17] on the vagus (mechanical production of pressure neuritis), and also of the procedure long ago practiced by Langley[18] and recently by Cannon[19] in the neck nerves (phrenicosympathicus anastomosis).

Timme, by placing a ligature very gently around each of the vagus trunks above the diaphragm on cats, succeeded in producing a hyperplasia of the mucous membrane in the stomach (on the other hand no increase, but rather a decrease in the function of the stomach). By cutting the phrenic and sympathetic nerves on one side of the neck of a cat, and sewing together the proximal end of the former with the distal (head) end of the latter, Langley obtained a satisfactory union of these two heterogeneous nerves, but did not, even after

15. MacCallum and Cornell: Med. News, Oct. 15, 1904.
16. Jonnesco: Tr. XIII Cong. internat. de méd., Paris, 1900. MacCallum and Cornell (Footnote 15).
17. Timme: Jour. Nerv. and Ment. Dis., 1913, xl, 311.
18. Langley: Jour. Physiol., 1898, xxiii, 240.
19. Cannon: Am. Jour. Physiol., 1915, xxxvi, 363.

197 days, observe any changes in pupil, etc., of the corresponding eye, that might point to a functional disturbance of the muscles supplied by the sympathetic. Cannon, however, claims to have observed this in at least one animal within five months after the nerve operation.

In two dogs I exposed one *cervical sympathetic ganglion,* transfixed and *ligated* it, *but not very tightly.* The operation on the first animal was performed Dec. 5, 1914. Its general condition was very good until death ensued, December 14; the cause of death was pneumonia. The other dog was operated on Jan. 16, 1915 and died, also of pneumonia, March 23. Toward the end the latter animal showed falling out of hair all over the body, emaciation, weakness, and (March 19) a sugar tolerance of less than 5.[20] The pulse rate did not rise (March 19 and 20 it was constant at about 100), and bladder urine was free from albumin and sugar at necropsy. Postmortem the stomach proved to be unusually large, and the thyroid microscopically rather rich in colloid.

In these two dogs I could *not,* notwithstanding almost daily examinations, observe *any* other *eye changes* on the side on which operation was performed than those usually produced by sympathetic paralysis, that is, contraction of the pupil and lid-cleft and, in the first few weeks, enophthalmos. Such an effect was what one would naturally have expected for the period following ligation; it was evidence that the nerve connection in the sympathetic had been broken. But it would seem that symptoms of irritation (pressure neuritis) should have been discernible later. The sixty-four-day period during which the second dog lived after ligation is, however, too short a time to justify any final inferences. Although the entire absence of any visible evidence of sympathetic irritation is striking, a longer period of observation might have led to a different result.

In my last series of experiments, discussed in this paper, I cut both the phrenic and sympathetic nerves on one side of the neck and *sewed together,* end to end, *the proximal end of the phrenic and the distal end of the sympathetic* (or the upper sympathetic ganglion). The operation was performed on four dogs, two cats and one rabbit. Of these, five died within twenty days after operation (of intoxication from narcosis, infection, postoperative hemorrhage, pneumonia). One dog was killed 111 days,[21] one cat 175 days later. I shall give a more detailed statement of these experiments in another paper. Suffice

20. That is, saccharose, administered by mouth in doses of 5 gm. per kilogram body weight, gave positive Nylander and Benedict tests during the following twenty-four hours. The physiologic tolerance for saccharose in tests on unoperated dogs was found by Goetsch, Cushing and Jacobsen to be on an average 10 gm. per kilogram body weight (Bull. Johns Hopkins Hosp., 1911, xxii, 165).

21. Included as No. 12 in the table.

it here to say that *in no case* was I able to find *any eye symptoms* that could be attributed to a sympathetic stimulation transferred to the smooth muscles of the orbit or of the eyeball. A contraction of the corresponding pupil and a drawing forward of the nictitating membrane continued throughout the period of observation, indicating that the sympathetic nerve had been interrupted. I had daily occasion to observe that no bulging of the eyeball or widening of lid-cleft, or the like, developed. I did not neglect to make repeated precise observations of the behavior of the pupil in broad daylight as well as in direct light. Never was I able to observe any enlarging of the pupil corresponding to the animal's respiration, which Cannon had found in a cat similarly operated on.

This concludes my report on the attempts to produce exophthalmos experimentally. Considered together, they show that whenever they proceeded from the assumption of cooperation through sympathetic stimulation, they were negative; but that in that group of cases in which paraphenylenediamin injections were made for the purpose, they were positive, even when the cooperation of the sympathetic had been eliminated. Thus far they have proved that an exophthalmos — one not resulting from an intra-orbital tumor, or some such cause— may arise without any intermediation of the cervical sympathetic. But we are by no means justified in transferring these results directly to human beings with exophthalmic goiter. On the contrary, it seems to me that my investigations show, among other things, how necessary it is to refrain from erroneous combinations. The temporary but slight forward shift of the bulb which, at least in certain animals, is likely to be produced by a direct electric stimulation of the cervical sympathetic is one thing, the somewhat more lasting protrusio bulbi in dogs after a subcutaneous paraphenylenediamin injection is quite another matter; and exophthalmos in exophthalmic goiter, sometimes continuing for years and occasionally of extremely pronounced character, has peculiarities that make it also a distinct group.

There is much to be said against the assumption that exophthalmos in exophthalmic goiter may be the result of a sympathetic stimulation. The entire aspect of the eye changes in paraphenylenediamin intoxication as a rule makes the impression of disturbance of the circulation, edema, which is by no means the most striking feature of exophthalmic goiter — although there are some similarities between them that are worthy of note (such as palpebral edema occasionally arising in exophthalmic goiter[22]).

22. See Case 9 in the exophthalmic goiter material, previously presented by me (Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, xxvii, 42).

On the whole, the question of the genesis of exophthalmos in exophthalmic goiter remains unsolved. Yet it must seem all the more desirable that we should acquire a thorough understanding of it, now that we have arrived at a more complete recognition of the importance of distinguishing clearly, both in diagnosis and prognosis, between the syndrome of clinical and pathologic anatomic phenomena which we roughly speak of as exophthalmic goiter.

THE CLINICAL STUDY OF EDEMA BY MEANS OF THE ELASTOMETER*

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The elastometer, an instrument devised by Schade[1] to measure edema, promises to change the study of edema from a subjective one depending on the amount of pitting obtained on pressure, to an objective one, whereby the degree of edema may be expressed in exact terms. Tactile estimation of edema fails not only to give an accurate idea of fluctuations that occur in an edematous area, but by the tactile sense alone, slight and even moderate degrees of edema may pass unnoticed. Indeed, Widal[2] has shown that in the adult an increase in weight up to 6 kilos may occur before edema will be sufficiently marked to be noted by the palpating finger. This figure varies in different individuals under different conditions. Studies in water retention, which have heretofore been done by noting the changes in the body weight or by determining the fluid intake and output, may now be improved by controlling such studies with estimation of edema obtained by the elastometer, for by means of this instrument, one can detect degrees of edema not appreciable by the palpating finger.

Principle of the Instrument.—(Figure 1.) A disk mounted on a perpendicular tactile rod is placed on the skin surface, with the addition of a superimposed weight; the amount of depression caused by the sinking of the weighted disk into the skin and subcutaneous tissue is graphically transferred by a writing lever to a revolving drum, making a characteristic curve. Surrounding this tactile disk, which measures the elasticity, is a set of three similar tactile disks, which rest on the surrounding skin surface, and indicate by a separate lever on the revolving drum any movement of the central disk other than that caused by the addition or removal of the weight. This line is known as the control line and must be straight in order to have the record of any value. Thus, faulty curves caused by disturbing factors can be eliminated by observing the control line.

Method of Use.—To use the instrument it is necessary that the patient be absolutely quiet. The location selected for taking the reading may be any part of the body surface overlying a bony area. Thus, the dorsal fold of the wrist, the forehead, or the lower part of the leg above the malleolus, may be used in making these determinations. The dorsal fold of the wrist has been found to give the most satisfactory readings, since this part of the body is more easily put at complete rest than the other areas mentioned. The patient

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1. Schade, H.: Ztschr. f. Exper. Path. u. Therap., 1912, xi, 369.

2. Widal, F., and Lemierre, A.: Ergebn. der inn. Med. u. Kinderh., 1909, iv, 523.

may be either in the recumbent or sitting posture. The hand and forearm are surrounded by sand bags in such a manner as to give complete relaxation, yet be well immobilized and not interfere with the circulation. The patient must relax as completely as possible. It is almost impossible to obtain readings on patients who will not cooperate. The patient relaxed, the instrument is placed on the table close to the bedside, if the patient is recumbent, or placed on the same table as the extremity tested if the patient is in a sitting position.

The tactile disks are lowered until they come in contact with the skin surface, the disks being so arranged that the control disks surround the weight-bearing disk. This arrangement occasionally offers some difficulty, in that the writing points controlled by these two sets of tactile disks may come in close approximation on the drum surface, thereby hindering their independent

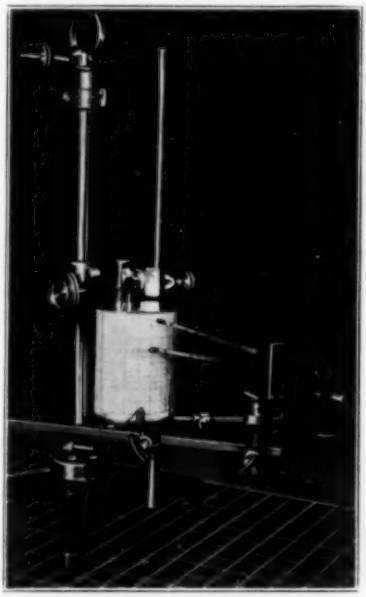

Fig. 1.—The elastometer.

working. Manipulation of the tactile disks is then necessary until the two writing points are separated and the movement of the one does not affect that of the other. The drum is then allowed to revolve. As soon as the lines drawn on the revolving drum are parallel and fairly horizontal, the weight is placed on the weight holder, which is a circular shelf attached to the central rod. These weights are of three sizes; 50, 75 and 100 gm., respectively. In our work, the 50 gm. weight has been used almost exclusively, because we found it gave the most satisfactory curves in the majority of cases. The 75 and 100 gm. weights are heavier than necessary to obtain successful readings in working with children.

Various degrees of elasticity give characteristic curves. Figure 2 represents diagrammatically extremes of variation in the curves that may be theoretically obtained. Curve 1 represents perfect elasticity. *a* is the base line. At the

point *x* the weight is added, whereupon the lever makes its ascent on the line b_1 which reaches its height rather quickly and continues along the line b_2. At the point *y*, the weight is removed and the lever falls rapidly and perpendicularly making the line c_1 and reaches its base line at c_2, which is on a level with the original base line *a*. Curve 2 represents a condition present in a severe edema. At the point *x*, the weight is added, whereupon the lever rises rapidly along the line b_1 but soon changes to a slow sloping ascent, making the line b_2. This slow curved ascent is due to the gradual sinking in of the tactile disk into the inelastic tissue. When the weight is removed at *y*, the lever descends along the line c_1 as the tactile disk rises from its depression but soon reaches its lowest point and descends no further, on account of the depression formed in the inelastic tissue remaining ("pitting"). The line c_2 remains, therefore, some distance from the original base line, this difference representing the loss of elasticity. Curve 3 represents the opposite condition from elasticity, namely, plasticity. At the point *x*, the weight is added, and the lever ascending slowly makes the line *b*. At the point *y*, the weight is removed but on account of the plasticity, the tactile disk remaining in the

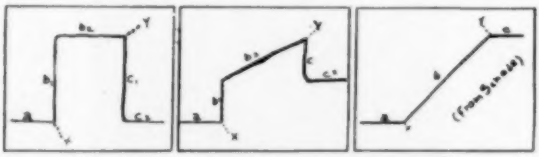

Fig. 2.—Diagrammatic representation of curves that may be theoretically obtained by the elastometer. Full description given in the text.

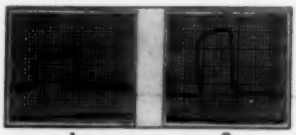

Fig. 3.—Height of curve varying with amount of subcutaneous tissues.

depression formed, the lever does not descend but continues along the line *c*. Not only is the degree of elasticity expressed by the difference between the line c_2 and the original base line, but by the character of the ascending and descending curves.

In our early work with the instrument, following Schade, we expressed readings in percentages. We have found that variation in percentages may result from relative changes in the various tactile disks on the skin surface, causing a difference in the height of a curve. Rearrangement of the tactile disks on the skin surface may place the curve-forming disk on a part having a greater amount of subcutaneous tissue, which would give a greater height to the ascent curve. Hereby it may occur that with the change in the height of the curve there may be associated a change in the elasticity expressed in percentage. This becomes a very important yet uncontrollable factor in the comparison of readings taken from two separate parts of the body or on two separate individuals. Thus, a reading on the leg would give a higher curve than one on the wrist, and it may happen that the percentage loss of elasticity on the leg is greater than on the wrist, despite the fact that there is a palpable edema on the wrist and not on the leg.

Figure 3 illustrates a difference in the height of the curves depending on a rearrangement of tactile disks. In this case there is no loss of elasticity. A large amount of subcutaneous adipose tissue may give abnormal curves not dependent on elasticity loss.

The curves obtained by the elastometer in individuals with normal elasticity (Fig. 4) show a rapid perpendicular ascent, an almost horizontal upper line, and a perpendicular descent line, the base of the last line being on a level with the original base line or becoming so within a minute.

Following Schade, we have taken a one minute interval as the standard time in which the curve is formed, and allow one minute after the removal of the weight for the return to the base line. When on taking a reading at a certain point a faultless curve is not obtained, due to the patient's movements or other causes, the tactile disks should be moved, since depression in the skin formed by immediate previous readings may affect the character of subsequent readings obtained from that part. Figure 5 shows three succcessive readings taken on the same point without moving the tactile disks. The first curve shows a definite loss of elasticity, the second and third curves show less loss, taking the preceding return line as the base line.

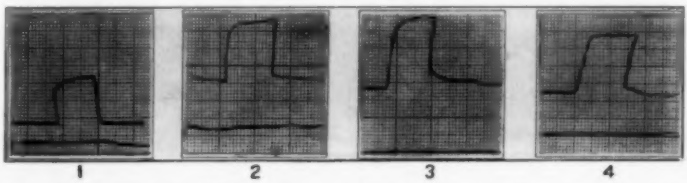

Fig. 4.—Normal elasticity curves, readings taken at wrist. Curve 1, T. H., neurasthenia; Curve 2, N. F., chronic endocarditis; Curve 3, F. O., chronic endocarditis; Curve 4, S. R., contracture of foot.

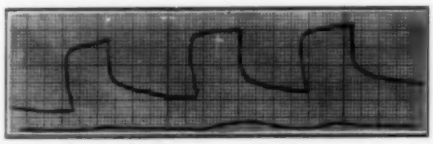

Fig. 5.—Successive readings taken on same point without rearranging disks. Wrist readings.

OBSERVATIONS

In edema resulting from general causes, such as that associated with cardiac insufficiency or nephritis, while, by ordinary palpation, this edema may seem to confine itself to a definite locality such as the face or extremities, the elastometer will usually show a more generalized loss of elasticity. Figure 6 shows readings taken on the wrists of patients who showed no palpable edema at the wrist, but had palpable edema at some other part of the body. With a severe edema present in any part of the body, readings taken at the wrist will generally show slight or moderate losses of elasticity, which will usually persist even after the palpable edema in the distant part has disappeared (Fig. 7).

Curve 1 is a reading taken on the forehead of a patient with a chronic endocarditis, who had a postscarlatinal nephritis at the time of the reading. The face showed a marked edema, which was not only palpable but visible. The urinalysis at this time showed a large amount of albumin, hyaline and granular casts. The reading in the curve is the characteristic one of a severe edema, the sloping gradual ascent and the deficient return to the base line on removal of the weight. Curve 2 was taken nearly a month later when the patient exhibited no palpable edema on any part of the body and the urine was free from casts and albumin. Despite the entire disappearance of palpable edema, the wrist shows a slight loss of elasticity.

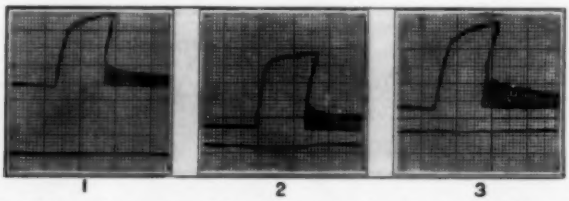

Fig. 6.—Edema demonstrated by elastometer though not palpable when reading is taken. Curve 1, hydrothorax; no palpable edema any part of body. Reading at wrist. Curve 2, nephritis, chronic; edema palpable in lower extremities. Reading at wrist. Curve 3, endocarditis, mitral, chronic. Moderate edema of lower extremities. Reading at wrist.

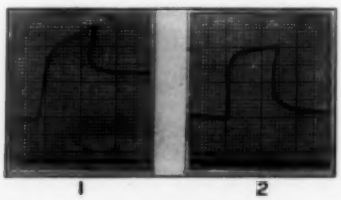

Fig. 7.—A. K., Curve 1. Forehead. Palpable and visible edema. (Dec. 11, 1914.) Curve 2. Wrist. No palpable edema over any part of body. (Jan. 4, 1915.)

In patients with nephritis we have observed persistent elasticity loss even after the disappearance of all other symptoms. Curve 2, Figure 8, shows a reading taken on a patient with chronic nephritis. This patient had previously presented symptoms of a uremic character, at which time there was a generalized palpable edema, ascites, excretion of urine for a few days almost approaching anuria, phenolsulphonephthalein excretion 15 per cent. in two hours. The patient slowly improved and at the time the reading was taken showed no evidence of any trouble except the faintest trace of albumin and the elasticity

loss exhibited in the curve. The patient was discharged, but since then has been readmitted with palpable edema and the usual urinary findings of a chronic nephritis.

In one other similar case of nephritis, a gradually diminishing but persistent elasticity loss was succeeded by a recurrence of the other symptoms which had entirely disappeared. In these cases the elastometric readings served as a helpful gauge of the progress of the disease.

It is probable that with the improvement of the instrument and the technic of its use, such readings will assume important clinical value.

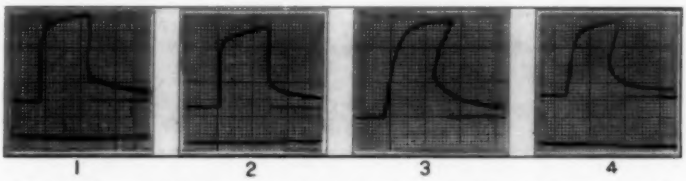

Fig. 8.—Curve 1, J. T.; Curve 2, A. J.; Curve 3, W. S.; Curve 4, S. G.

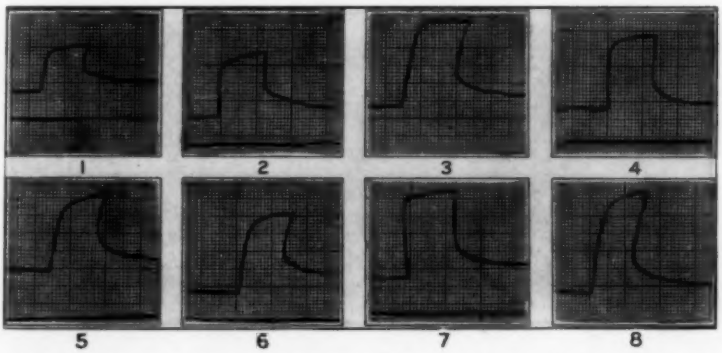

Fig. 9.—Upper line readings taken on right wrist; lower line readings taken on left wrist. Left to right dated December 6, December 9, December 14, December 26.

The manifestation of palpable edema in chronic endocarditis has usually been associated in our minds with serious disturbances of cardiac functions. With the elastometer, slight changes in elasticity are demonstrable in numerous cases of endocarditis without other evidence of decompensation. Curve 1, Figure 8, is a reading obtained on a patient with a mitral endocarditis. This patient was admitted to The Children's Memorial Hospital following a first attack of mitral endocarditis. On admission the patient had painful joints, and the exam-

ination of the heart showed the presence of a soft systolic apical murmur transmitted toward the axilla. At the time the reading was taken there were no subjective or objective signs of a break in compensation. The heart action was regular and strong. The mitral murmur was present as on admission. The patient felt well, and appeared normal. The reading taken at the wrist, however, shows a slight loss of elasticity. Curve 4, Figure 8, is a reading taken on a patient with chronic mitral and aortic endocarditis who at no time showed any palpable edema. Urinalysis was negative. The reading taken at the wrist shows a slight loss of elasticity. Curve 3, Figure 8, illustrates well the known

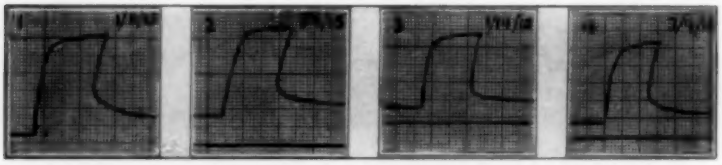

Fig. 10.—A. R., endocarditis, mitral, chronic.

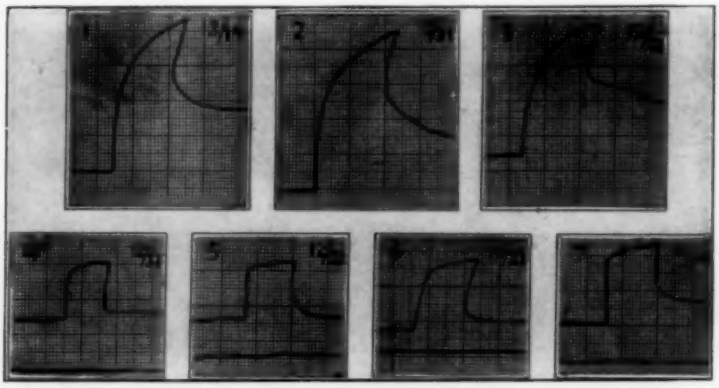

Fig. 11.—Upper row above malleolus. Lower row at wrist.

occurrence of edema in anemia. The patient had been in the hospital on several occasions for hemophilia. At the time the reading was taken the patient was in the hospital on account of subcutaneous hemorrhages following injury. Blood examination showed the following:

Red cell count	3,980,000
White cell count	6,600
Hemoglobin (Sahli)	31 per cent.

The red cells show moderate achromia and quite a bit of anisocytosis. The elastometric reading taken on the wrist shows definite loss of elasticity though the edema is not palpable.

Figure 9 shows readings taken in a case of hydrothorax with general reduced tissue turgor and palpable edema over the chest. This patient was admitted to The Children's Memorial Hospital Dec. 5, 1914. The Roentgen-ray examination corroborated the diagnosis of hydrothorax. Heart and urine were normal. Von Pirquet reaction was positive.

Dec. 6, 1914.—Elastometric reading on both wrists show a decided loss of elasticity. Curve 1, Figure 9.

Dec. 9, 1914.—Tissue turgor somewhat improved. The elastometric reading shows little change. Curve 2, Figure 9.

Dec. 14, 1914.—Very slight palpable edema of lower extremities. Elastometric reading, Curve 3, Figure 9. (Little change.)

December 19, 1914.—Thoracentesis done; 6 ounces greenish-yellow fluid removed. Cultures negative.

Dec. 26, 1914.—No palpable edema. Curve 4, Figure 9. Turgor much improved.

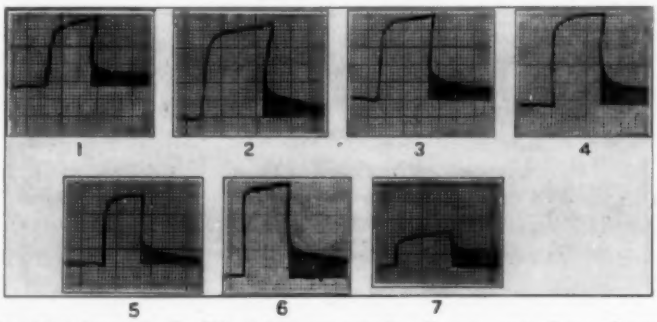

Fig. 12.—Curve 1, P. W., lobar pneumonia, 21 per cent. loss; Curve 2, G. R., pulmonary tuberculosis, 15 per cent. loss; Curve 3, E. H., nephritis, 12 per cent. loss; Curve 4, J. H., lobar pneumonia, 20 per cent. loss; Curve 5, F. D., unknown infection, 7 per cent. loss; Curve 6, T. C., pericarditis, 19 per cent. loss; Curve 7, L. N., miliary tuberculosis, 44 per cent. loss.

With improvement of the tissue turgor, with diminution of the fluid in the pleural cavity, with decline of the temperature curve, the elastometric readings show a gradual return to normal. The upper line of readings was taken on the right wrist, the lower line on the left wrist, at neither of which parts was there at any time any palpable edema.

We have further data on cases of pneumonia, to be published later, indicating an interrelationship between fever and edema.

Figure 10 is a series of readings taken on a patient with chronic mitral endocarditis. This patient was admitted to The Children's Memorial Hospital, Dec. 5, 1914, at which time there was no palpable edema.

Jan. 7, 1915.—Child appears much worse. Face puffy. Edema palpable over sacrum and very slightly over tibiae. Breathing labored and noisy, patient restless, and has a cyanotic pallor.

Jan. 8, 1915.—Elastometric reading at wrist shows a decided loss of elasticity.

Jan. 9, 1915.—Elastometric reading shows similar findings.

Jan. 12, 1915.—Child somewhat better; breathing is quieter. Following restriction of fluids and active catharsis, edema of face has diminished. Feet and sacrum still show slight palpable edema.

Jan. 14, 1915.—Elastometric reading shows less edema than on January 9.

March 9, 1915.—No palpable edema. Patient comfortable. Elastometric reading shows still some loss of elasticity persisting.

Here, again, the elastometer not only recorded fluctuations in the amount of edema, but showed the presence of edema, after its subjective perception was absent.

Figure 11 shows a series of readings taken on a patient with marked palpable edema of the feet from an unknown cause (cirrhosis of liver?). The three upper readings, showing the usual curve of a severe edema, were taken just above the malleolus. The lower line of readings taken on the wrist show a gradually increasing elasticity loss; Curves 4 and 5 show very slight evidence of edema, but Curves 6 and 7 show quite distinct losses of elasticity. At no time did the wrist show any palpable edema.

Figure 12 illustrates the mathematical expression of edema. The shaded portion represents the deficient return of the base line. Each small square on the figure represents a millimeter. The percentage loss of elasticity is obtained by dividing the number of millimeters between the return line and base line (one minute after removal of the weight) by the height of the curve expressed in millimeters.

DISCUSSION

It is here seen that by means of the elastometer, the study of edema becomes a more accurate one. Though, with the present instrument, the expression of edema in mathematical terms is not deemed advisable, the character of the curves, together with the deficiency of return to the base line permit of an approximate estimation of the intensity of an edema.

Furthermore, the instrument makes possible the recognition of slight degrees of edema which heretofore could not be detected. Persistent evidence of elasticity loss, despite the disappearance of other signs in patients with nephritis or endocarditis, indicates the advisability of more prolonged observation of cases of this character.

THE URIC ACID SOLVENT POWER OF URINE AFTER ADMINISTRATION OF PIPERAZIN, LYSIDIN, LITHIUM CARBONATE AND OTHER ALKALIES *

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In a recent paper[1] I reported the results of an investigation of the uric acid dissolving power of hexamethylenamin. The mode of action of that drug is quite different from that of the rest of those substances which have been classed as "uric acid solvents." The latter, if they act at all as solvents, do so by virtue of being basic substances. The purpose of this paper is to report an investigation of the solvent power of the most important members of this class.

The organic compounds piperazin and lysidin are amine derivatives, and the nitrogen of their molecules imparts to these substances a basic character so that they combine with acids. They are supposed to form salts with uric acid which are very soluble. And it is true that in aqueous solution they dissolve a very large amount of uric acid (see Table 10).

Lithium carbonate and sodium bicarbonate are supposed to act as alkalies toward uric acid, forming lithium and sodium urates which are quite soluble. In aqueous solution they certainly do cause a considerable quantity of uric acid to go into solution (Table 10).

Furthermore, each of these four solvents when added to urine or phosphate mixture, causes the urine to take up much more uric acid than it could dissolve without the addition of the drug (Tables 8 and 9). It remains to be determined, therefore, whether after administration of these drugs the urine acquires a greater uric acid solvent power than normal urines of similar character (as regards concentration and acidity) would have; in other words, whether the drug is excreted in such form and concentration as to show demonstrable uric acid solvent action due to the drug itself. This is what we have tried to determine.

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* From the Department of Biochemistry, Medical School, University of Oregon.

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1. Haskins, H. D.: THE ARCHIVES INT. MED., 1915, xvi, 1055.

TABLE 1.—URINES AFTER TAKING A DRUG—

LESS DILUTE URINES AFTER PIPERAZIN

Acidity	Dosage Gm.	Time Hours	Piper. Test	Uric Acid Content Mg.	Total Uric Acid Mg.	Uric Acid Dissolved Mg.
7.4*	2×2	0-2	+	71.36	612.48	541.12
7.3*	2	2-4	Trace	90.36	695.32	604.96
7.3*	2	0-2	..	43.63	484.94	441.31
7.2*	2	0-1¼	+	22.80	367.90	345.10
6.9	2	0-3½	+	62.24	664.92	602.68
6.9	2	2-3	+	16.64	309.24	292.60
6.9	2	0-2	+	75.92	288.72	212.80
6.9	2	0-3	+	80.24	203.60	123.36
6.85	2	3-4	+	12.08	214.24	202.16
6.75	2	3-4¼	..	18.87	221.53	202.66
6.2	2	0-2¼	+	79.72	500.00	420.28
....	..	.....	..	.....	.....	.....
6.0	2	0-5½	+	63.00	115.44	52.44
5.8	2	0-2	+	30.32	116.96	86.64

TABLE 2.—

DILUTE URINES AFTER PIPERAZIN

6.9	1	0 - ½	.....	9.20	94.00	84.80
....	..	.....	.....	.....	.....	.....
6.55	1	½-1¾	.....	8.40	48.20	39.80
6.5	2	4 -5½	.....	23.20	82.00	58.80
6.5	1×2	1 -1½	.....	9.20	61.20	52.00
6.5	2	1½-2	.....	10.00	60.40	50.40
6.45	1×4	0 - ½	.....	7.60	19.60	12.00
6.4	1×4	¾-1¾	.....	9.20	44.40	35.20
6.35	1	0 -1	.....	10.44	47.44	37.00
6.3	1×4	1½-2	.....	9.20	43.60	34.40
....	..	.....	.....	.....	.....	.....
6.25	1×3	¼- ¾	.....	8.40	18.00	9.60
6.1	2	3¼-4¼	.....	10.00	52.80	42.80
6.1	2	½-1½	.....	9.20	26.00	16.80
6.0	2	0 -2½	.....	7.52	55.40	47.88
6.0	2	2 -2¾	.....	8.40	25.20	16.80

TABLE 3.—

LESS DILUTE URINES AFTER LYSIDIN

7.1	2×2	½-2½	.....	38.00	178.00	140.00
7.1	2×2	5 -6	.....	112.40	200.00	87.60
6.1	2	0 -1	.....	31.60	68.40	36.80
6.0	2×2	2½-4	.....	22.00	51.60	29.60
5.85	2	0 -3	.....	56.92	130.64	73.72
5.85	2×2	0 - ½	.....	52.00	71.60	19.60
5.8	2	0 -4½	.....	63.76	109.36	45.60
5.8	2	0 -2¼	.....	78.96	101.76	22.80

—CONTROLS. URINES WITHOUT THE DRUG

LESS DILUTE CONTROL URINES

Uric Acid Dissolved Mg.	Total Uric Acid Mg.	Uric Acid Content Mg.	Acidity	Remarks
283.14	296.94	13.80	7.6*	*$NaHCO_3$ administered.
350.00	446.55	96.55	7.3*	
255.75	360.75	105.00	7.3*	
223.50	279.00	55.50	7.2*	
198.40	247.60	49.20	7.0	
159.20	282.00	122.80	6.9	
158.84	230.20	71.36	6.9	
102.76	137.26	34.50	6.9	
154.40	216.40	62.00	6.8	
148.00	198.00	50.00	6.7	
31.20	75.60	44.40	6.4	
15.20	72.40	57.20	6.3	
8.80	34.00	25.20	6.1	†A very exceptional control.
40.56	76.20	35.64	5.9†	

—TABLE 2.—*(Continued)*

DILUTE NORMAL URINES

141.75	150.08	8.33	6.9	The drug seems to begin to be excreted very soon and to be present in the urine in appreciable amount for at least four hours.
111.75	120.00	8.25	6.9	
47.95	62.91	14.96	6.55	
63.92	76.16	12.24	6.5	
49.58	59.28	9.70	6.5	
50.80	66.00	15.20	6.5	
51.48	59.04	7.56	6.45	
31.20	38.80	7.60	6.4	The urines in this table are too dilute to give tests for the drug.
22.94	30.42	7.48	6.35	
33.75	41.25	7.50	6.3	
19.20	31.60	12.40	6.3	
19.50	27.06	7.56	6.25	
.....	.....	.....	...	
.....	.....	.....	...	
37.92	52.33	14.41	6.0	
12.00	22.00	10.00	6.0	

—TABLE 3.—*(Continued)*

LESS DILUTE CONTROL URINES

172.00	244.40	72.40	7.1	
135.42	185.82	50.40	7.1	
8.80	34.00	25. 20	6.1	
.....	.....	.....	...	
40.56	76.20	35.64	5.9*	*A very exceptional control.
.....	.....	.....	...	
.....	.....	.....	...	
.....	.....	.....	...	

The citrates and acetates of sodium and potassium are converted in the body into bicarbonate, so that their effect on the urine should be the same as that of sodium bicarbonate. It seemed advisable, however, to test sodium citrate experimentally so as to make sure of the effectiveness of this class of salts.

While conducting a research on atophan, its uric acid solvent power was determined incidentally, although there was no reason to suppose that it belonged to the class of uric acid solvents. I take this occasion to report the results. The urines from eight persons (twenty-four-hour samples) were of low enough acidity to lead to the expectation that they might dissolve extra uric acid. Their content of uric acid ranged from 80 to 132 mg. in 100 c.c. Only one of the urines took up any uric acid, however; this had an acidity of 6.8 and dissolved 46 mg., which was less than a normal urine of that acidity would be expected to dissolve. The indications are, therefore, that atophan may interfere with the solvent action of the urine.

The urines reported in the tables were all from normal individuals. They are not as numerous as we had hoped to secure, since few persons were willing to take these drugs.[2] Hospital urines were not obtainable.

The methods used in the present investigation were identical with those reported in the paper on hexamethylenamin. The results of our work are given in the tables where comparison is made of the uric acid dissolved by the drug urines with that dissolved by normal urines of similar acidity and concentration. In interpreting our results we take it for granted that the drug urine must show distinctly greater solvent power than the control normal urines, in order to permit us to argue that the drug plays any part in the solvent action.

The figures for uric acid are given as milligrams in 100 c.c. of urine. "Uric acid content" means the amount present in the urine as passed. "Total uric acid" means the amount present in the filtrate after shaking the urine with pure uric acid for twenty minutes at 37 C. The difference between these two is the "uric acid dissolved." This last is the index of the solvent power of the urine.

In the cases in which more than one dose of the drug was taken, the time interval for secretion of the urine was calculated from the time of taking the last dose.

In Table 9 the acidity figures are those of the phosphate mixture (NaH_2PO_4 and Na_2HPO_4 mixed as in urine) before any drug was added. The drugs rendered the solutions alkaline. In Table 10, on the other hand, the acidity figures are those of the solutions of the drugs.

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2. The author wishes to express his gratitude to those, students and others, who did assist him so materially in this respect, foremost among whom were Dr. P. J. Hanzlik, Dr. R. J. Collins and C. J. Friedman. The assistance of Mr. Friedman in all the work of the research was invaluable.

In connection with Table 8, attention must be called to the fact that the urines of the same acidity are not different urines but portions of the same urine. The effect of the drugs in changing the reaction of the urine is of sufficient interest to report (Table 11).

COMMENT ON THE TABLES

In the case of the dilute ... ues (Tables 2 and 4) after taking piperazin and lysidin, the results are not significant, possibly because dilution of the drug reduces its effect so that no conclusion as to solvent action can be drawn.

In Table 1 are found some very striking results. The first, second, third and fifth urines dissolved an excessive amount of uric acid, much beyond our expectations of what could be dissolved by any substance excreted into the urine. The sixth urine shows a high result for a urine of an acidity 6.9. Even though the solvent action be due in part to the bicarbonate taken also, yet there can be no doubt whatever that the piperazin has been excreted in sufficient quantity to exert a very decided solvent action.

It is true that the 2 gm. doses are extratherapeutic, but we see no reason why the maximum therapeutic dose should not have a distinct effect, at least when the urine is not dilute and is not acid in reaction.

In the case of lysidin, the two alkaline urines, the first two of Table 3, do not show sufficient solvent action to be able to attribute any of it to the drug. The dosage being equal to the maximum therapeutic dose, we expected to secure evidence of some solvent action if there was enough action to be worth considering.

We knew of no way of determining whether lysidin is excreted either unchanged or as a derivative which could be effective as a uric acid solvent.

The results in Table 8 indicate that lysidin ought to be an effective solvent provided it is excreted unchanged and rapidly enough to give a proper concentration in the urine. We may also add the qualifying statements as in the case of piperazin, that the urine should not be dilute nor acid in reaction.

We would not expect that the basic compounds, piperazin and lysidin, could show any solvent action in acid urines, yet several surprising results are to be found in Tables 1 and 3. The eleventh urine in Table 1, of 6.2 acidity, took up 420 mg. of uric acid, a result which is quite remarkable. Several more acid urines showed distinct solvent power beyond what we have ever secured with normal urines of those acidities. These are the last urine of Table 1 (5.8 acidity, 86 mg. dissolved), and the fifth (5.85 acidity, 73 mg. dissolved) and seventh (5.8 acidity, 45 mg. dissolved) urines of Table 3. Our experience with normal urines has led us to expect no solvent action whatever if the

TABLE 4.—

DILUTE URINES AFTER LYSIDIN

Acidity	Dosage Gm.	Time Hours	Uric Acid Content Mg.	Total Uric Acid Mg.	Uric Acid Dissolved Mg.
6.75	2×2	0 - ¾	14.00	121.20	107.20
6.35	1×4	¾-1½	8.40	52.40	44.00
6.35	1×4	0 - ¾	7.60	43.60	36.00
6.3	2×2	3¾-5	10.80	42.80	32.00
6.2	1×4	1½-2½	8.40	62.00	53.60
6.1	1×2	0 - ¾	7.60	58.00	50.40
6.0	1	0 - ¾	10.80	59.60	48.80
6.0	1×4	2½-4	9.20	43.60	34.40
6.0	2	2 -3	9.20	26.00	16.80

TABLE 5.—URINES AFTER ADMINISTRATION OF ALKALIES—

LESS DILUTE URINES AFTER LITHIUM CARBONATE

Acidity	Dosage Gm.	Drug	Uric Acid Content Mg.	Total Uric Acid Mg.	Uric Acid Dissolved Mg.
7.0	†	Li_2CO_3	50.80	176.40	125.60
6.85	†	Li_2CO_3	29.20	142.00	112.80

TABLE 6.—

DILUTE URINES AFTER LITHIUM CARBONATE

7.6	1.0	Li_2CO_3	15.40	244.34	228.94
7.2	1.0	Li_2CO_3	19.33	421.52	402.19
....	.....	.....	.....	.....	.....
....	.....	.....	.....	.....	.....
....	.....	.....	.....	.....	.....
7.15	0.5×2	Li_2CO_3	12.40	114.80	102.40
7.0	0.5×2	Li_2CO_3	18.40	136.50	118.10
6.95	†	Li_2CO_3	12.40	214.80	202.40
6.95	†	Li_2CO_3	13.20	159.60	146.40
6.95	†	Li_2CO_3	11.60	145.20	133.60
6.9	0.5×2	Li_2CO_3	9.20	142.00	132.80

TABLE 7.—

LESS DILUTE URINES AFTER SODIUM SALTS

7.6	4	$NaHCO_3$	13.80	296.94	283.14
7.3	4	$NaHCO_3$	96.55	446.55	350.00
7.3	4	$NaHCO_3$	105.00	360.75	255.75
7.3	3	Sod. citrate	70.50	283.87	213.37
7.3	3	Sod. citrate	129.24	313.85	184.61
7.25	3	Sod. citrate	56.00	227.20	171.20
7.25	3	Sod. citrate	72.00	222.26	150.26
7.2	2	$NaHCO_3$	55.50	279.00	223.50
7.2	3	Sod. citrate	52.02	218.94	166.92
7.15	3	Sod. citrate	27.00	210.41	183.41
7.1	2	Sod. citrate	30.57	197.88	167.31

—TABLE 4.—*(Continued)*

DILUTE NORMAL URINES

Uric Acid Dissolved Mg.	Total Uric Acid Mg.	Uric Acid Content Mg.	Acidity	Remarks
83.00	91.25	8.25	6.75	These drug urines are too dilute doubtless to show solvent action due to the drug.
48.75	68.40	19.65	6.4	
22.94	30.42	7.48	6.35	
33.75	41.25	7.50	6.3	
7.20	22.80	15.60	6.2	
.....	.....	.....	...	
37.92	52.33	14.41	6.0	
12.00	22.00	10.00	6.0	
14.82	25.50	10.68	5.95	

—CONTROL URINES

LESS DILUTE CONTROL URINES

Uric Acid Dissolved Mg.	Total Uric Acid Mg.	Uric Acid Content Mg.	Acidity	Remarks
187.60	240.00	52.40	7.0	†1.5 gm. in 1 L. water taken in one day.
131.20	174.00	42.80	6.8	

—TABLE 6.—*(Continued)*

DILUTE CONTROL URINES

144.75	154.50	9.75	7.3	* Urines containing bicarbonate.
157.29	172.25	14.96	7.1	
283.14	296.94	13.80	7.6*	
350.00	446.55	96.55	7.3*	
255.75	360.75	105.00	7.3*	
.....	.....	.....	...	
118.40	138.80	20.40	7.0	
105.66	122.16	16.50	6.95	† (As above.)
141.75	150.08	8.33	6.9	
130.07	139.06	8.99	6.9	
111.75	120.00	8.25	6.9	

—TABLE 7.—*(Continued)*

LESS DILUTE CONTROL URINES

.....	.....	.....	...	All of these urines showed presence of bicarbonate.
.....	.....	.....	...	
.....	.....	.....	...	
.....	.....	.....	...	
.....	.....	.....	...	
188.50	234.34	45.84	7.2	
188.16	250.08	61.92	7.2	
.....	.....	.....	...	
182.04	238.36	56.32	7.2	
172.00	244.40	72.40	7.1	
162.40	207.60	45.20	7.0	

acidity was as great as 5.8 or 5.9 and the urine was not dilute. The control urine given in Tables 1 and 3, 5.9 acidity 40 mg. dissolved, stands out as the sole (and unexplained) exception.

We have no explanation to offer as to how it is possible for piperazin and lysidin to show uric acid solvent power in these acid urines, but we can not avoid the conclusion that these results are very striking evidence that such solvent power exists.

Although we admit that lysidin may impart to the urine solvent properties due to the drug, we do not consider it practical to use it, because of the enormous dosage that would be necessary in order to secure pronounced effects comparable to the effect of piperazin.

Piperazin, however, would seem to be especially suitable for securing an intense uric acid solvent action, provided very large doses are given for a short time, together with sodium citrate or bicarbonate (so that the urine is alkaline).

The acid urines which we obtained after administration of alkalies are not reported in Tables 5, 6 and 7 for the following reason: The fact that the urine remains acid shows that the alkali has been neutralized in the body and is being excreted in the form of a salt. The only chance for the alkali increasing the solvent power of the urine in such a case would be by causing an increase in the amount of monohydrogen phosphate, and such increase would have but a moderate effect, resulting in no greater uric acid solvent power than could be duplicated by normal urines.

A massive uric acid solvent action, however, is shown by some alkaline urines, probably because they bring about colloidal solution of the uric acid. Schade and Boden[3] secured colloidal solutions of uric acid by using aqueous solutions of alkalies. Such an action is shown apparently by the second urine of Table 6 (7.2 acidity, 402 mg. dissolved). This is the only significant result with lithium carbonate. The solvent action is greater than we have secured with urines rendered alkaline by giving sodium bicarbonate or citrate. Having secured toxic symptoms in two persons taking lithium, we did not attempt to use very large doses nor to give it to many individuals. We are certain that lithium carbonate is not effective in smaller doses than those used by us. There is no real reason for giving it, since it is much safer to use the sodium salts.

Table 7 shows that the sodium salts give a sufficiently marked and a very reliable uric acid solvent action, whenever they have rendered the urine at least faintly alkaline. We can not see why any other drugs should ever be chosen in preference to them.

3. Schade and Boden: Ztschr. f. physiol. Chem., 1913, lxxxiii, 347.

TABLE 8.—Effect of Drugs Added to Urine

Acidity	Drug Added	Per Cent. of Drug	Control Uric Acid Dissolved (No Drug) Mg.	Uric Acid Dissolved (After Drug Was Added) Mg.	Excess of Uric Acid Dissolved Due to the Added Drug Mg.
5.0	Piperazin	0.680	0.00	233.32	233.32
6.24	Piperazin	0.125	19.50	99.84	80.34
6.0	Piperazin	0.132	27.30	103.74	76.44
5.8	Piperazin	0.085	19.00	47.12	28.12
5.8	Piperazin	0.142	19.00	78.28	59.28
5.8	Piperazin	0.170	19.00	85.12	66.12
5.8	Piperazin	0.200	19.00	103.36	84.36
5.8	Piperazin	0.230	19.00	120.08	101.08
5.8	Piperazin	0.260	19.00	152.76	133.76
6.0	Lysidin	0.050	27.30	60.84	33.54
6.0	Lysidin	0.100	27.30	99.06	71.76
6.0	Lysidin	0.200	27.30	186.42	159.12
5.0	Lysidin	1.000	0.00	129.96	129.96
5.0	Li_2CO_3	0.157	0.00	245.48	245.48
5.0	$NaHCO_3$	1.000	0.00	288.80	288.80

TABLE 9.—Effect of Drugs Added to Phosphate Solution

6.8	Piperazin	0.500	120.00	274.00	154.00
6.8	Piperazin	1.000	120.00	511.40	391.40
6.8	Li_2CO_3	0.168	138.24	340.40	202.16

TABLE 10.—Effect of Drugs Added to Water

....	Piperazin	0.50	8.4	250.80	242.40
7.25	Piperazin	0.65	8.4	541.80	533.40
....	Piperazin	1.00	8.4	527.60	519.20
7.4	Lysidin	1.00	8.4	455.92	447.52
7.4	Li_2CO_3	0.16	8.4	503. 80	495.40
7.25	$NaHCO_3$	1.00	8.4	484.80	476.40

TABLE 11.—Acidity of the Urine as Affected by Drugs

Before the Drug	After the Drug	Drug Used	Per Cent.
5.0	7.4	Piperazin	0.68
5.0	7.1	Lysidin	1.0
5.0	7.1	Li_2CO_3	0.157
5.0	6.8	$NaHCO_3$	1.0
5.8	6.0	Piperazin	0.085
5.8	6.25	Piperazin	0.142
5.8	6.55	Piperazin	0.17
5.8	6.85	Piperazin	0.20
5.8	6.95	Piperazin	0.23
5.8	7.2	Piperazin	0.26

We called attention in the previous paper to the favorable effect of dilution of the urine. Probably the greatest total solvent action would be secured by combining diuresis from heavy drinking of water with the alkalization of the urine by sodium bicarbonate or citrate.

Whenever normal urine becomes alkaline and it contains a considerable concentration of metal ions as a result of the diet, it will show marked uric acid solvent action, exactly as it would if sodium bicarbonate had been taken and for the same reason. Blatherwick[4] has also observed this fact. We have found that normal alkaline urines always contain bicarbonate as well as the alkaline urines passed after taking sodium citrate or bicarbonate.

CONCLUSIONS

1. Piperazin can cause the urine to dissolve more uric acid than it would without the drug, and this effect is most marked if sodium citrate or bicarbonate be also given and if diuresis be avoided.

2. Lysidin can act as a uric acid solvent but is not a practical therapeutic agent because of the large doses required.

3. Lithium carbonate is a uric acid solvent if large enough doses are used, but is unsafe and possesses no advantage over sodium citrate or bicarbonate.

4. Sodium citrate and bicarbonate are reliable and satisfactory uric acid dissolving agents when given in such dosage as to keep the urine alkaline.

761 Lovejoy Street.

4. Blatherwick, N. R.: THE ARCHIVES INT. MED., 1914, xiv, 409.

SEROLOGIC EXAMINATIONS IN A CASE OF POLYCYTHEMIA *

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DETROIT

Recently Lucas[1] in an exhaustive article on erythremia reviewed the literature in a comprehensive manner, adding two new cases to the series. It is apparent that a greater number of cases of polycythemia with chronic cyanosis and with or without splenomegaly are being recognized.

Among the various theories advanced as to the cause of erythremia, the one originally suggested by Rendu and Widal,[2] and later amplified by Osler[3] and Weber,[4] ascribes the changes that take place to unusual erythropoietic activities. Pathological findings have, in a measure, substantiated this explanation, though Saundby and Russell[5] describe normal bone marrow findings in their case. If we are to accept this view of primary excessive formation of red cells in the bone marrow, we have an analogy to myelogenous leukemia, in which the leukoblastic activity dominates the picture. In contrast stands this notable feature of erythremia—the absence of erythroblasts in the circulating blood.

The theory advanced by Belonovsky,[6] that the enlarged spleen elaborates a small amount of hemolysin, enough to excite a hyperactivity of the bone marrow and thereby raise the total number of red cells, as well as the hemoglobin, has also many facts to substantiate it. The occurrence of some cases of idiopathic polycythemia without splenomegaly, as in this instance, leaves us to seek another source of toxin that might have such limited hemolytic activity.

A theory that has had numerous supporters and positive reports to substantiate it has ascribed an increased resistance to hemolysis to

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* Submitted for publication Dec. 22, 1915.

1. Lucas, Walter S.: THE ARCHIVES INT. MED., 1912, x, 597.
2. Rendu and Widal: Bull Soc. méd. d. hôp., Series 3, 528. Quoted from Osler's article in the Am. Jour. Med. Sc., 1903, cxxvi, 187.
3. Osler, W.: Bull. Johns Hopkins Hosp., 1903, xix, 91; also, Am. Jour. Med. Sc., 1903, cxxvi, 187.
4. Weber, F. P.: Proc. Roy. Soc. Med., London, 1908-09; also, Internat. Clin., 1905, iv, 47.
5. Saundby and Russell: Lancet, London, 1902, i, 515.
6. Belonovsky: Quoted from Lucas' work. See Note 1.

the erythrocytes. Guinon, Rist and Simon[7] state that the red cells of their patient resisted hemolysis. Parkes Weber[4] reports one case with the resistance to hemolysis about normal.

This patient presented the opportunity for a careful serologic study. This was undertaken with the view of determining the following questions:

1. The resistance of polycythemic cells to hemolysis.

2. The possible presence of antihemolysin or anticomplementary substances.

3. The presence of complement in the polycythemic serum.

4. A comparison of complements from the serum of known normal individuals and the polycythemic serum.

5. The fragility of the polycythemic cells.

The patient on whom this study was made presented himself for examination in September, 1912, and has been under almost constant supervision since. Like several previously reported cases this man was a Russian Jew, an interesting fact perhaps in the etiology. This patient's blood count on the first examination was hemoglobin, 123 per cent., Sahli. Red blood cells, 7,920,000; white blood cells, 6,900. Differential counts showed nothing abnormal. No nucleated forms or myelocytes were seen. The urine was normal. The patient did not react to tuberculin. The Wassermann was negative. Heart and lungs were normal and there was no evidence of glandular enlargement. The spleen could not be palpated on deep breathing. Blood pressure, 140 systolic, 80 diastolic. Roentgenograms of the heart and mediastinum negative.

One of the first things observed in comparing the polycythemic blood with normal blood is the difference in serum and cellular content. Equal quantities of polycythemic and of normal blood were compared. It was found that the polycythemic patient's blood yields but one-half the amount of serum that the normal does.

PROTOCOL 1

Complement, c.c.*	Amboceptor, c.c.†	One Per Cent. Suspension Normal Human Cells, c.c.‡	Result
0.6	0.5	1	Complete hemolysis
0.5	0.5	1	Complete hemolysis
0.4	0.5	1	Partial hemolysis

* 10 per cent. guinea-pig serum.
† 1 unit = 0.007 c.c. Dilute to 0.5 c.c.
‡ Normal saline to 2.5 c.c.; incubate at 37.5 C. 30 minutes.

Protocol 1.—Preliminary titer showing the amount of 10 per cent. guinea-pig complement required to produce complete hemolysis of 1 c.c. of a 1 per cent. suspension of normal human red cells.

7. Guinon, Rist and Simon: Bull et. mém. Soc. d. hôp. de Paris, 1904, xxi, 786.

PROTOCOL 2

Complement, c.c.*	Amboceptor, c.c.†	One Per Cent. Suspension Polycythemic Cells, c.c.‡	Result
0.6	0.5	1	Complete hemolysis
0.55	0.5	1	Complete hemolysis
0.5	0.5	1	Complete hemolysis
0.45	0.5	1	Partial hemolysis
0.4	0.5	1	Partial hemolysis
0.35	0.5	1	Slight hemolysis

* 10 per cent. guinea-pig serum.
† 1 unit = 0.007 c.c. Dilute to 0.5 c.c.
‡ Normal saline to 2.5 c.c.; incubate at 37.5 C. 30 minutes.

Protocol 2.—Using 1 c.c. of a 1 per cent. suspension of polycythemic red blood cells with varying amounts of the complement dilution we find 0.5 c.c. of complement produces complete hemolysis as in Protocol 1. This shows that the polycythemic cells are not unusually resistent to hemolysis.

PROTOCOL 3

Complement, c.c.*	Amboceptor, c.c.†	Polycythemic Serum, c.c.‡	One Per Cent. Suspension Polycythemic Cells, c.c.§	Result
0.6	0.5	0.25	1	Complete hemolysis
0.5	0.5	0.25	1	Complete hemolysis
0.4	0.5	0.25	1	Partial hemolysis

* 10 per cent. guinea-pig serum.
† 1 unit = 0.007 c.c. Dilute to 0.5 c.c.
‡ Double amount required for hemolysis. Inactivate at 56 C. 30 minutes.
§ Normal saline to 2.5 c.c.; incubate at 37.5 C. 30 minutes.

Protocol 3.—The addition of relatively large amounts of polycythemic serum which had been inactivated at 56 C. for one-half hour did not inhibit the hemolysis of the polycythemic cells.

PROTOCOL 4

Complement, Polycythemic Serum, c.c.	Amboceptor, c.c.*	One Per Cent. Suspension Polycythemic Cells, c.c.†	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis
0.15	0.5	1	Complete hemolysis

* 1 unit = 0.007 c.c. Dilute to 0.5 c.c.
† Normal saline to 2.5 c.c. Incubate at 37.5 C. 30 minutes.

PROTOCOL 5

Complement, Polycythemic Serum, c.c.	Amboceptor, c.c.*	One Per Cent. Suspension Normal Human Cells, c.c.†	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis
0.18	0.5	1	Complete hemolysis

* 1 unit = 0.007 c.c. Dilute to 0.5 c.c.
† Saline to 2.5 c.c. Incubate at 37.5 C. 30 minutes.

Protocols 4 and 5.—Comparison of Protocols 4 and 5 shows that equal amounts of normal human and polycythemic red cells require equal amounts of polycythemic serum used as complement to produce complete hemolysis.

PROTOCOL 6

Case A, Complement, Normal Serum, c.c.	Amboceptor, c.c.*	One Per Cent. Suspension Normal Cells, c.c.†	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis

* 1 unit = 0.007 c.c. Dilute to 0.5 c.c.
† Saline to 2.5 c.c. Incubate at 37.5 C. 30 minutes.

Case A, Complement, Normal Serum, c.c.‡	Amboceptor, c.c.*	One Per Cent. Suspension Polycythemic Cells, c.c.†	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis

* 1 unit = 0.007 c.c. Dilute to 0.5 c.c.
† Saline to 2.5 c.c. Incubate at 37.5 C. 30 minutes.
‡ The above was repeated using serum of four other healthy adults and gave identical results.

Protocol 6.—The serum of healthy normal adults was taken and used as complement for comparison with the polycythemic serum. The complement contained in normal serums hemolyzed normal red cells and polycythemic cells in the same quantities and at the same rate as did the complement contained in the polycythemic serum.

PROTOCOL 7

Per cent. saline solution*	0.1	0.2	0.3	0.4	0.5	0.6		4	5	6	7	7.5	8	9	10
Complete hemolysis	+	+	+	..	..	..	..	..	..	..	..	±	±	+	+
Slight hemolysis	..	..	..	+	±	..	..	..	±	+	+				
No hemolysis	..	..	..	..	..	+	++	+							

* The above results were obtained using polycythemic and normal red blood cells.

In all the hemolytic experiments a 1 per cent. suspension of washed corpuscles taken from a normal healthy adult was used. The quantity used throughout all the work was 1 c.c. The normal red cells and the polycythemic cells were centrifugalized at the same speed and for equal periods of time, thereby making certain that both suspensions were of equal strength. The amboceptor unit was 0.007 c.c. diluted so that 0.5 c.c. of the dilution was equal to one unit.

FRAGILITY EXPERIMENTS

For the purpose of determining whether or not the red blood cells of the polycythemic patient were more or less resistant than normal individual's cells to hypertonic and hypotonic saline solution, the following tests were carried out: Blood from the polycythemic and normal individual was removed from the median basilic vein and mixed with an equal volume of 2 per cent. citrate solution. Two drops of each were then placed in the saline solutions of varying dilutions with results as indicated in Protocol 7. It is evident from this test that the cells of the polycythemic patient are neither more nor less fragile than the cells of the control individual.

CONCLUSIONS

1. Quantitatively the polycythemic patient has approximately one-half the amount of complement that a normal adult has.

2. Qualitatively the complements from the polycythemic patient and from normal adults are of equal potency.

3. The polycythemic serum contains no anticomplementary bodies.

4. The polycythemic red cells are neither more nor less fragile than red cells from normal adults.

5. Polycythemic and normal red cells are equally resistant to hemolysis.

ON THE TOXICITY OF VARIOUS COMMERCIAL PREPARATIONS OF EMETIN HYDROCHLORID *

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In view of the widespread use of emetin hydrochlorid in the treatment of amebic dysentery and of pyorrhea alveolaris, more precise knowledge of the toxicity of the commercial preparations employed is highly desirable. The following case reports forcibly emphasize this fact:

CASE 1.—I. B. (Med. No. 33209), white, male, aged 56, a native of Baltimore, was admitted to the surgical service Oct. 12, 1914, complaining of an "ulcerated rectum." Fifteen years previously he had had a chancre, followed by a secondary eruption. For the past six years there had been alternating periods of diarrhea and constipation, with blood in the stools at times.

Examination.—On examination, there was found slight enlargement of the heart to the left, a soft systolic murmur at the apex and some impairment of the percussion note over the manubrium. The systolic pressure was 150 mm. Hg; diastolic, 70. The urine was negative. The blood showed: red blood corpuscles, 5,720,000; white blood corpuscles, 7,350; hemoglobin (Sahli), 92 per cent. The differential count was normal. The Wassermann reaction was positive. Actively motile amebas were found in the stool, and October 20 the patient was transferred to the medical service with a diagnosis of lues and amebic dysentery.

At this time the stools contained a few pus cells and a little mucus, but repeated examinations revealed no amebas. Sigmoidoscopic examination showed no ulceration or bleeding points; 10 cm. from the anus there were two small scars, probably of healed erosions. There was a considerable number of small internal hemorrhoids.

During the first three weeks of his stay in the hospital the patient was having only one or two stools daily. November 5, however, diarrhea developed; on the fifteenth he had eleven bowel movements. No amebas were found.

Treatment and Course.—November 17, subcutaneous injections of emetin hydrochlorid were begun. Three times a day, from the seventeenth to the twenty-fifth, inclusive, the patient received ½ grain; on the twenty-sixth and twenty-seventh, ⅓ grain; and from November 28 to December 5, inclusive, ½ grain. A few days after beginning the emetin treatment the number of stools became less. The improvement, however, was only temporary, and on November 26 there were nine, and December 3, eighteen stools in the twenty-four hours. It is noteworthy that December 10, five days after the emetin was discontinued, the diarrhea permanently ceased.

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* Submitted for publication Nov. 22, 1915.

* From the Medical Clinic of the Johns Hopkins Hospital.

* Eight of the ten original tracings accompanying this article were lost by the engravers. The records appearing in Figures 1, 2, 3, 4, 5 and 8 have been supplied by the authors in this emergency. They do not illustrate the various points brought out in the paper as satisfactorily as did the originals, inasmuch as they represent tracings which had previously been discarded.

December 4, a trace of albumin and a few granular casts appeared in the urine. Gastric analysis showed slight subacidity.

December 8, the phthalein excretion was 18 per cent. in two hours. Two days later, the nonprotein nitrogen of the blood was 112 mg. per 100 c.c.; the urea nitrogen, 92 mg. Sellards' test[1] revealed the existence of a high grade acidosis.

The amount of albumin in the urine gradually increased, and December 11, (four days before death) blood appeared. The patient was now slightly dyspneic and complained of nausea and pain in the umbilical region. On the fourteenth, the pulse was weak and rapid, the breathing was of the Cheyne-Stokes variety and coarse râles were heard throughout the chest. The leukocytes had risen to 14,600. The systolic blood pressure, which before had ranged from 150 to 190 mm. Hg, had fallen to 95.

December 15, after a period of marked dyspnea, the patient collapsed and died.

The lipase content of the blood obtained at necropsy was 1.4 per cent.

NECROPSY REPORT (DR. H. N. STEVENSON)

Anatomical Diagnosis.—Syphilitic aortitis; chronic aortic endocarditis; dilatation of the heart; chronic passive congestion of the viscera; arteriosclerosis; chronic indurative colitis; healed tuberculosis of the lung and hilic glands; bronchopneumonia.

Abstract of Notes.—Lungs: Diffuse bronchopneumonia. *Liver:* Lobulation distinct; irregular patches of congestion; no focal areas of necrosis. Microscopically, the lobulation is well defined; the cells in the periportal zones are large and granular. Cells in central portion of lobules are atrophic and widely separated by congested capillaries. *Spleen:* Not enlarged; shows congestion. *Kidneys:* Weight, 150 gm. each. Cortex about 5 mm. in thickness. Striations somewhat irregular and slightly distorted. Glomeruli indistinctly seen as minute, reddish, translucent dots of irregular intensity. Pyramids show slight congestion. Pyramidal striations are regular. Pelvis of each kidney shows some ecchymoses. Microscopically, the arteries show slight intimal thickening. There are a few ill-defined areas in the cortex where there is slight increase in interstitial tissue, and a few areas of round cell infiltration. *Duodenum:* Lymphoid elements slightly hyperplastic. No ulceration. *Ileum:* Slight flushing of mucosa in its lower portion. *Large Intestine:* The lumen is of the usual circumference. The mucosa is everywhere uniform in appearance, there being no erosions or ulcerations. It is of a uniformly pale gray, almost white, color, and the folds of the mucosa are indistinct. The mucosa gives the impression from its consistence of being thicker than normal. The mucous membrane of the rectum is slightly flushed, and microscopically shows marked infiltration by connective tissue and round cells.

SUMMARY.—A man weighing 153 pounds (69.5 kg.) received, daily, subcutaneous injections of emetin hydrochlorid over a period of twenty days. The average daily dose was 1½ grains (90 mg.),[2] or 1.3 mg. per kg. *In toto,* he received 29 grains (1.74 gm.), or 25 mg. per kg.

A previously existing diarrhea was at first apparently somewhat ameliorated, then markedly intensified. On the sixteenth day of treat-

1. Sellards, A. W.: Bull. Johns Hopkins Hosp., 1914, xxv, 101.

2. Throughout this paper 1 grain is regarded as the equivalent of 60 milligrams, inasmuch as the dosage of the commercial preparations is calculated on this basis.

ment the patient complained of nausea and abdominal pain. Albuminuria and cylindruria appeared and gradually increased. Finally there was evidence of acute renal insufficiency, with blood in the urine and diminution in the 'phthalein output, along with an increase in the nonprotein nitrogen of the blood. There was marked acidosis, as evidenced by the positive Sellards test. Bronchopneumonia and vasomotor collapse terminated the picture.

CASE 2.—A. G. E. (Med. No. 33818), a white woman, aged 31, was admitted to the medical service, March 4, 1915, complaining of attacks of nervous sick headache. These attacks, which she had had since childhood, presented all the essential features of migraine. Pigmentation of the arms after exposure to the sun, and occasional attacks of diarrhea following indiscretions in diet, had suggested to her physician the possibility of pellagra, but no evidence was found in support of this diagnosis.

Examination.—On examination, she was seen to be a thin, pale woman with well-marked pyorrhea alveolaris and gingivitis. The blood showed a profound secondary anemia. Repeated examinations of the stools revealed no ova or parasites, even after the administration of vermifuges. The gastric analysis was normal. A faint trace of albumin noted in the urine on the first examination soon disappeared. No casts were observed.

Treatment and Course.—At the suggestion of the dental department, ½ grain of emetin hydrochlorid was administered subcutaneously each day for four days, beginning April 2. April 3 the patient had a slight chill, followed by an elevation of temperature to 101. April 4 a distressing diarrhea began; there were ten bowel movements during the night. She complained of aching all over, of pain in the back and abdomen, and of tenesmus. The stools at this time contained large numbers of leukocytes and a few red blood cells. No amebas were found. The leukocytes rose to 13,800. During the following six days there were from five to ten stools in the twenty-four hours, all containing pus and blood. April 9, albumin reappeared in the urine. April 11, six days after discontinuing the emetin, the diarrhea promptly stopped, and did not recur during her stay in the hospital. The albuminuria also disappeared.

Stool cultures, pelvic and protoscopic examinations were negative. Following the onset of the diarrhea, a toxic delirious state developed, with great mental confusion and visual and auditory hallucinations, necessitating the transfer of the patient to the Phipps Psychiatric Clinic. In the course of a week the psychosis cleared up, and she was discharged mentally and physically much improved.

A letter from her husband received July 15 states that "she is in better shape than she has been for twelve years; she weighs 110½ pounds—more than she has ever weighed in her life."

A second letter was received, October 1, saying that save for an occasional attack of migraine, and a feeling of weakness on exertion, the patient was doing well.

SUMMARY.—An anemic, undernourished woman, weighing 95 pounds (43.2 kg.), received subcutaneously ½ grain of emetin hydrochlorid daily for four days. An intense diarrhea developed, associated with abdominal pain and tenesmus, which ceased six days after discontinuing the emetin treatment. At the same time she was in a toxic delirious state, which lasted for one week. She recovered rapidly and left the hospital much improved.

The daily dose of emetin was ½ grain (30 mg.) or 0.7 mg. per kg. Two grains (120 mg.) were given in toto, or 2.77 mg. per kg.

The symptoms here following emetin administration were quite out of proportion to the moderate dosage employed, and the particular preparation was suspected of being unusually toxic. Accordingly, a dog weighing 10.5 kg. was given 10 mg. subcutaneously daily for three days. On the third day a bloody diarrhea set in and the animal died on the same day. At necropsy, an extensive hemorrhagic gastro-enteritis was found. This dog received daily 1.0 mg. per kg., or, in toto, 3 mg. per kg.—approximately the same relative dosage as had been given to the patient. It will be seen from the experimental observations which follow that this particular preparation of emetin was decidedly more toxic than usual.

EXPERIMENTS ON ANIMALS

Studies were made on sixty-two animals, the series comprising dogs, cats and rabbits. Five commercial preparations of emetin hydrochlorid were investigated: Burroughs Wellcome & Co., (ampoules); Eli Lilly & Co., (ampoules); Merck & Co., (crystals); Parke, Davis & Co., (ampoules), and Sharp & Dohme, (hypodermic tablets).

Injections were made in part subcutaneously, in part intravenously. The points particularly observed were: (1) toxicity; (2) effects on the circulation and respiration; (3) pathological changes; (4) effect on the coagulation of the blood; (5) effect on renal function and the development of acidosis.

1. *Toxicity.* A. *Subcutaneous Injections.*—(See Table 1). Dogs receiving single small injections of 10 mg. (1 to 2 mg. per kg.) show no appreciable reaction. Repeated daily injections of 10 mg. cause death (usually with gastro-enteritis) in from three to fifteen days (average, seven to ten days). Either there is an actual cumulative action of the drug or an altered tissue response on the part of the animals.

Larger single subcutaneous injections of 30 to 45 mg. (3 to 5 mg. per kg.) cause death in from two to five days. The same gastro-intestinal lesions are found at necropsy.

Cats tolerate larger doses. Daily injections of from 2 to 5 mg. per kg. kill the animals in from seven to eleven days. As a rule, the anatomical lesions present are exceedingly slight. The results in kittens are essentially similar to those in adult cats.

In rabbits, daily doses of 5 mg. (3 to 4 mg. per kg.) are uniformly fatal in from five to six days. As in cats, necropsy usually reveals but slight anatomical changes.

TABLE 1.—SUBCUTANEOUS INJECTIONS

Species and Number of Animals Used	Preparation Used	Daily Dosage, Mg.	Daily Dosage, Mg. per Kg.	Total Dosage, Mg.	Total Dosage, Mg. per Kg.	Time Necessary to Kill, Days	Remarks
I. Dogs							
11	(A)	10	0.95 - 2.04 Av. 1.54	20 - 90 Av. 58.2	2.85 - 11.7 Av. 8.86	3 - 11 Av. 6.5	More than 50 per cent. of the animals vomited one or two days prior to death. Diarrhea accompanied the vomiting in about a quarter of the animals. The lowest figures in this series are those resulting from the use of the unusually toxic preparation mentioned in the second case report.
5	(B)	10	1.3 - 2.12 Av. 1.74	60 - 100 Av. 80	11.16 - 19.08 Av. 13.58	8 - 13 Av. 10.5	One animal alive but emaciated after nine days. Diarrhea and vomiting in only one instance. Same pathological lesions as with preparation (A). One animal (pregnant) had miscarriage on the tenth day, with birth of ten dead pups.
3	(C)	10	1.02 - 1.6 Av. 1.37	50 - 96 Av. 72	8 - 10.43 Av. 9.41	5 - 15 Av. 9.5	Vomiting and diarrhea one or two days prior to death in two of the animals. Usual lesions.
4	(A)	15 - 45	3.26 - 6.38 Av. 4.44	30 - 90 Av. 61.2	7.5 - 9 Av. 7.62	2 - 6 Av. 3	More acute poisoning. Same lesions. Vomiting and diarrhea usually on second day. Three of the animals died on second day. One, receiving the smallest doses, with two days' interval between injections, died on the sixth day.
II. Cats							
4	(A)	10	3.14 - 5.12 Av. 3.97	60 - 100 Av. 77.5	21.96 - 36.3 Av. 30.25	7 - 10 Av. 9.5	Vomiting and diarrhea on the second or third day preceding death in three animals. All drooled from the mouth when toxic symptoms became manifest.
2	(A)	2.5 - 5	2.17 - 5.55 Av. 3.0	12.5 - 27.5 Av. 20	13.88 - 23.9 Av. 18.89	4 - 7 Av. 5.5	These animals were kittens. Lively until day of death.
1	(B)	10	3.14	70	21.98	10	No vomiting or diarrhea.
4	(C)	10	2.0 - 5.26 Av. 3.22	60 - 100 Av. 85	16.0 - 29.4 Av. 23.5	9 - 15 Av. 11	Vomiting in two of the animals.
2	(D)	10	2.8 - 4.16 Av. 3.48	70 - 100 Av. 85	28 - 29.12 Av. 28.56	7 - 11 Av. 9	Diarrhea in one animal, vomiting in the other.
4	(E)	10	4.0 - 4.76 Av. 4.5	30 - 60 Av. 47.5	14 - 27.24 Av. 21.07	3 - 7 Av. 5.5	No diarrhea or vomiting. Marked drooling from the mouth for two or three days prior to death.
III. Rabbits							
2	(A)	5	3.22 - 3.33 Av. 3.27	20 - 25 Av. 22.5	13.32 - 16.1 Av. 14.71	5 - 6 Av. 5.5	Muscular tremors in one animal just before death; in tetanic spasm for a short while.
2	(C)	5	3.33 - 4.16 Av. 3.75	20 - 25 Av. 22.5	13.32 - 20.8 Av. 17.6	5	

Differences in the time necessary to kill are dependent in part on variations in toxicity of the preparations used, and in part, perhaps, on varying degrees of resistance to intoxication of individual animals. Whatever the cause, these variations are extreme. In dogs, for instance, a total dosage of 3 mg. per kg. of the most toxic preparation given subcutaneously killed within three days, whereas, 19 mg, per kg. of another commercial preparation required eleven days. In cats, 14 mg. per kg. (total dosage) of one preparation caused death in three days, whereas, 29 mg. per kg. of another killed only after seven days. For immediate death following intravenous administration, 4 mg. per kg. in one instance, and 18 mg. per kg. in another, were necessary.

The symptoms of intoxication as a rule manifest themselves two or three days before death. There is extreme muscular weakness and pronounced lethargy. The animals lie on their sides in the cages and are roused with difficulty. More than half of the dogs and cats vomit; many have numerous thin, unformed stools. Some of the dogs suffer from a bloody diarrhea; a few have large hemorrhages from the bowel on the day of death. Muscular tremors occur occasionally in dogs and rabbits. Drooling from the mouth is common, especially in cats.

B. *Intravenous Injections.*—(See Table 2). The lethal single intravenous dose is variable (4 to 18 mg. per kg. in dogs, 6 to 16 mg. per kg. in cats) and is largely dependent on amount, dilution and rapidity of injection. In exceptional instances, dogs may temporarily survive single injections of from 3.5 to 12 mg. per kg., but death generally occurs within two days.

Vedder[3] has found that "2.5 mg. per kg. intravenously is the minimum fatal dose for rabbits, while one rabbit died as the result of 20 mg. per kg. administered subcutaneously. The rabbits to which the drug was given intravenously died in a few seconds, apparently as the result of centric paralysis. 10 mg. per kg. subcutaneously on two successive days is a uniformly fatal dose for white rats."

2. *Effects on the Circulation and Respiration.*—Kymographic records were made with the animals under ether anesthesia and electrocardiograms were taken on chloretoned dogs.

The subcutaneous injection of a relatively large dose (40 mg.) in a dog weighing 10.2 kg. caused no appreciable fall in blood pressure within fifteen minutes; at the end of half an hour the pressure had dropped from 150 mm. to 100 mm. Hg. (See Fig. 1). This was probably due in part to the influence of the anesthetic. There was no change in the animal's general condition. Single smaller subcutaneous doses of 10 mg. (1 to 2 mg. per kg.) have no perceptible effects.

3. Vedder, E. B.: Jour. Am. Med. Assn., 1914, lxii, 501.

TABLE 2.—Intravenous Injections

Species and Number of Animals Used	Preparation Used	Total Dosage, Mg.	Amount of Dilution, c.c.	Total Dosage, Mg. per Kg.	Time Necessary to Kill, Days	Remarks
I. Dogs						
7	(A)	45 - 192 Av. 106.5	4 - 200 Av. 38	3.71 - 18.82 Av. 9.68	Immediate death	
2	(C)	80	5	9 - 9.3 Av. 9.15	Immediate death	
2	(D)	60 - 120 Av. 90	10 - 40 Av. 25	5.71 - 11.42 Av. 8.6	Immediate death	
1	(A)	60	12	4.18	1	Ventricular fibrillation with temporary spontaneous recovery. Bloody diarrhea on day of death. No vomiting. At necropsy, extensive hemorrhagic gastro-enteritis with ulcers in the duodenum and upper jejunum.
2	(C)	110 - 120 Av. 115	10 - 21 Av. 15.5	6.96 - 11.95 Av. 9.45	2 - 5 Av. 3.5	One of the animals received two injections of 60 mg. each, given at an interval of two days. Vomited on the third day and died with a bloody diarrhea on the fifth day. The other temporarily recovered from ventricular fibrillation, but died on the second day. At necropsy, gastro-enteritis.
1	(D)	60	10	4.91	2	No diarrhea or vomiting.
II. Cats						
3	(A)	20 - 40 Av. 27.3	3 - 25 Av. 11	6.02 - 16.66 Av. 9.94	Immediate death	

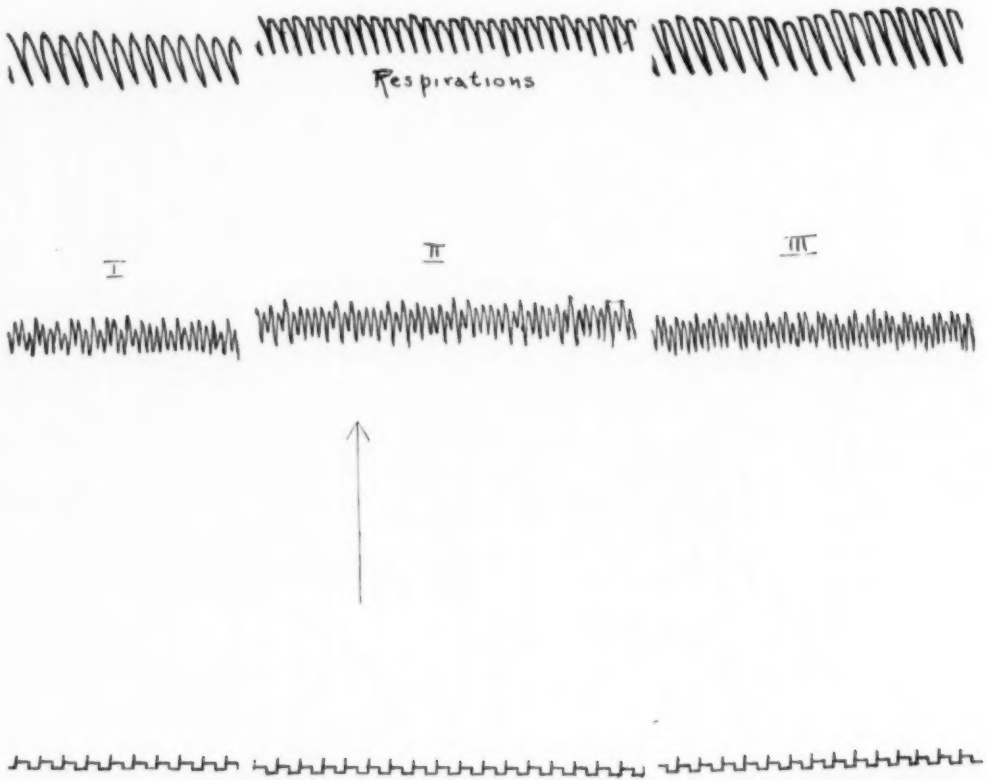

Fig. 1.—Dog. Weight, 10.2 kg. Subcutaneous injection of 40 mg. in 2 c.c. saline into thigh (3.92 mg. per kg.) I. Normal tracing. II. One minute later. Arrow marks end of injection. III. Twenty minutes later. Lower tracing in all the records marks time in seconds.

In slowly poisoned animals, subjects of repeated small daily subcutaneous injections (1 to 2 mg. per kg.), there is a marked fall in pressure[4] coincident with the appearance of toxic symptoms. In one animal of 5.5 kg. which received seven daily injections of 10 mg. each, there was a difference of 100 mm. between the original measurement and that taken on the day of death. The pulse in the sick animals is rapid and small.

The effect of intravenous injections depends on several factors: (1) the quantity injected; (2) its dilution; (3) the rate of injection, and to a lesser extent (4) the preparation employed; and (5) the individual susceptibility of the animal.

The first of these is obvious. Relatively small amounts (3 to 4 mg. per kg.) given in small volume (5 to 10 c.c.) and rapidly injected, cause an abrupt fall in blood pressure and death in a few minutes, heart and respirations stopping synchronously (Figs. 2 and 3). The lethal effect is due mainly to the toxic action of the drug on the heart muscle proper, causing an acute cardiac dilatation. Whether there is at the same time a vasomotor paralysis is not clear. The venous congestion of the abdominal organs suggests that this element may play a rôle.

On the other hand, when the emetin is well diluted and slowly administered, tremendous doses may be well borne. One dog weighing 10 kg. received 192 mg. in 200 c.c. of salt solution during a thirty-minute period. Death followed a final rapid concentrated injection (40 mg. in 10 c.c.). This animal received in all 18.82 mg. per kg.—an unusually large amount.

The various commercial preparations, as well as different lots from the same firm, vary somewhat in toxicity (Tables 1 and 2, and Case 2). Baermann and Heinemann[5] have made a similar observation. It is difficult to gauge accurately the extent of this variation, since animals, like human beings, apparently show differences in their individual tolerance for the drug.[6]

Following the intravenous injection of a non-lethal dose there is a prompt fall of blood pressure of from 20 to 140 mm. Hg, varying according to the conditions of the injection. The pressure rapidly returns to its former or even to a higher level. There may be recovery from alarmingly low pressures (Fig. 4).

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4. The apparatus devised by Dr. B. B. Turner was used in making these determinations. (See Turner, B. B., Marshall, E. K., Jr., and Lamson, P. D.: Jour. Pharmacol. and Exper. Therap., 1915, vii, 129).

5. Baermann, G., and Heinemann, H.: München. med. Wchnschr., 1913, lx, 1132 and 1210.

6. This is exemplified by variations in tolerance to crystallin emetin. (See Table 1, Cats, Preparation E.)

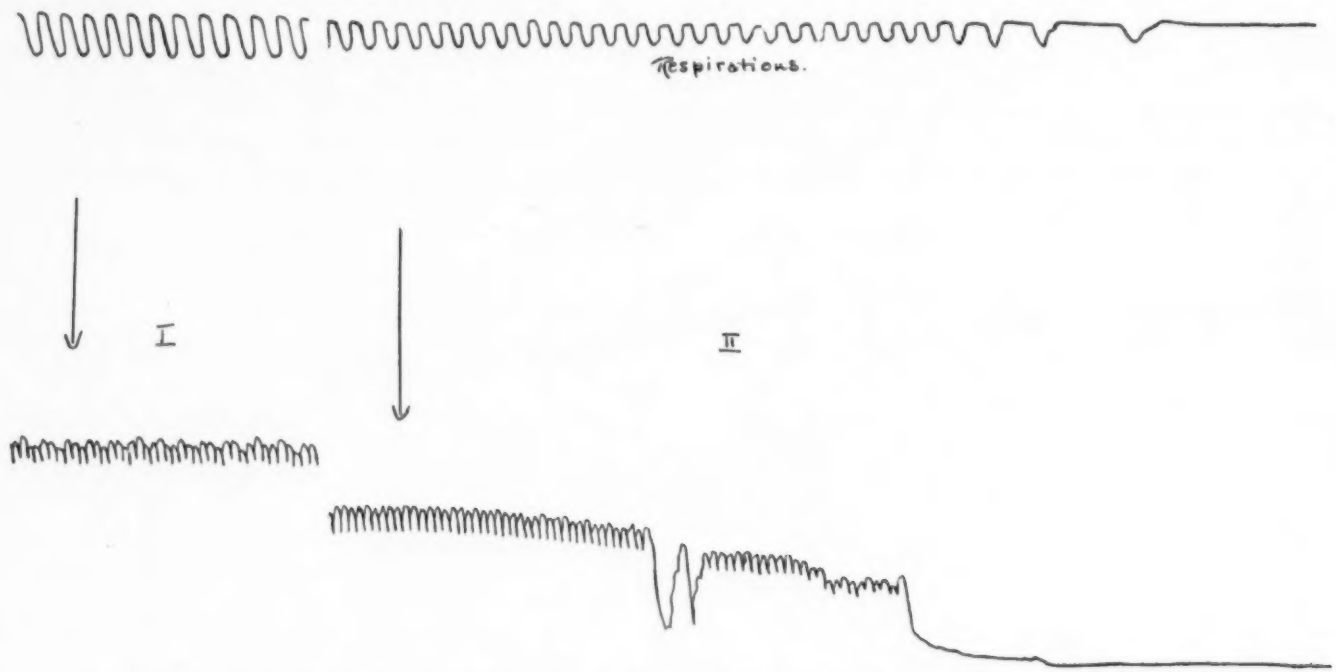

Fig. 2.—Dog. Weight, 10.5 kg. Intravenous injection of 60 mg. in 10 c.c. saline. (5.71 mg. per kg.) Duration of injection, 45 seconds. I. Normal tracing. Arrow marks beginning of injection. II. Forty-five seconds later. Arrow marks end of injection.

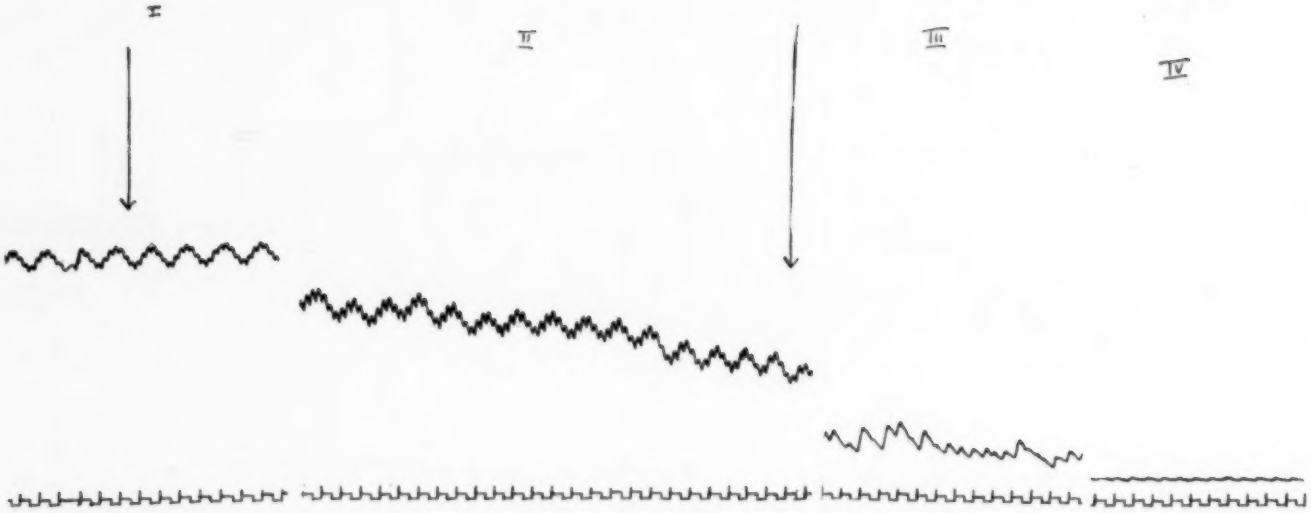

Fig. 3.—Cat. Weight, 2.8 kg. Intravenous injection of 20 mg. in 20 c.c. saline. (7.14 mg. per kg.) Duration of injection, 1 minute, 30 seconds. I. Normal tracing. Arrow marks beginning of injection. II. One minute later. Arrow marks end of injection. III. One minute later. IV. One minute later.

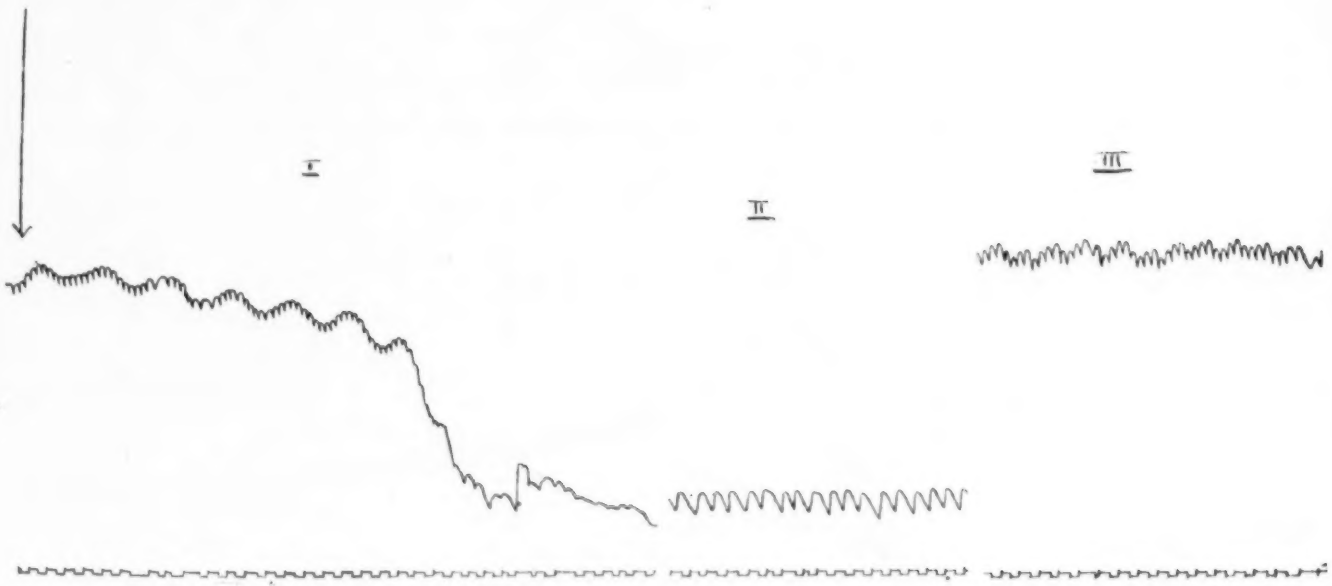

Fig. 4.—Dog. Weight, 8.5 kg. Intravenous injection of 20 mg. in 10 c.c. saline. (2.35 mg. per kg.) Duration of injection, 45 seconds. I. Arrow marks end of injection. II. One minute later. III. Two minutes later.

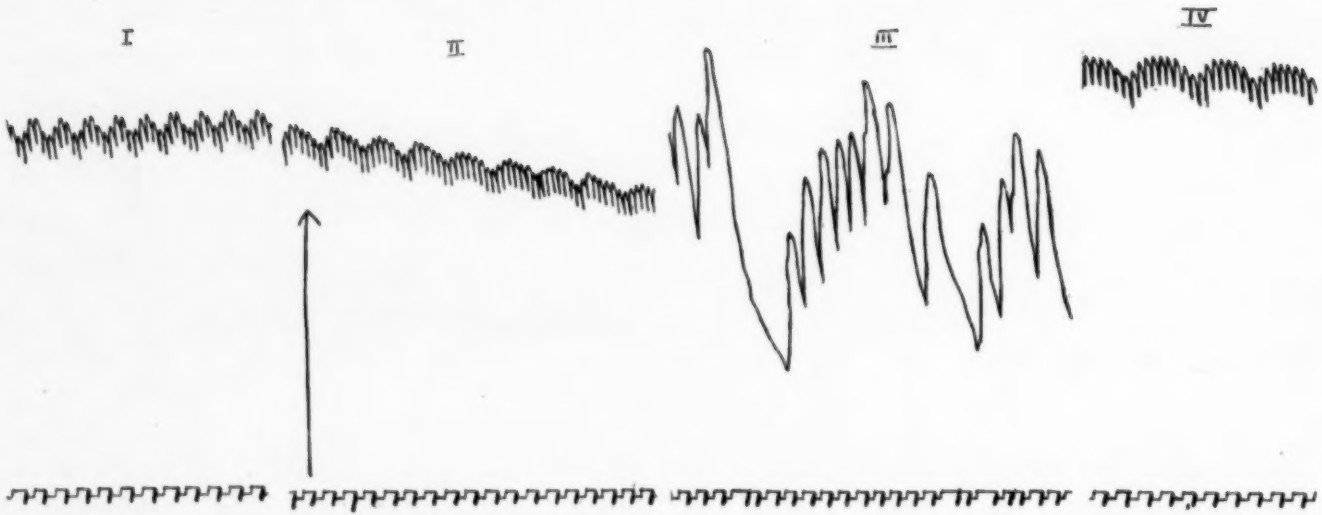

Fig. 5.—Dog. Weight, 14.35 kg. Intravenous injection of 60 mg. in 12 c.c. saline. (4.18 mg. per kg.) I. Normal tracing. II. Arrow marks end of injection, which lasted 2 minutes. III. Ventricular fibrillation, which continued for 5 minutes and 7 seconds. IV. Spontaneous resumption of normal rhythm at higher blood-pressure level.

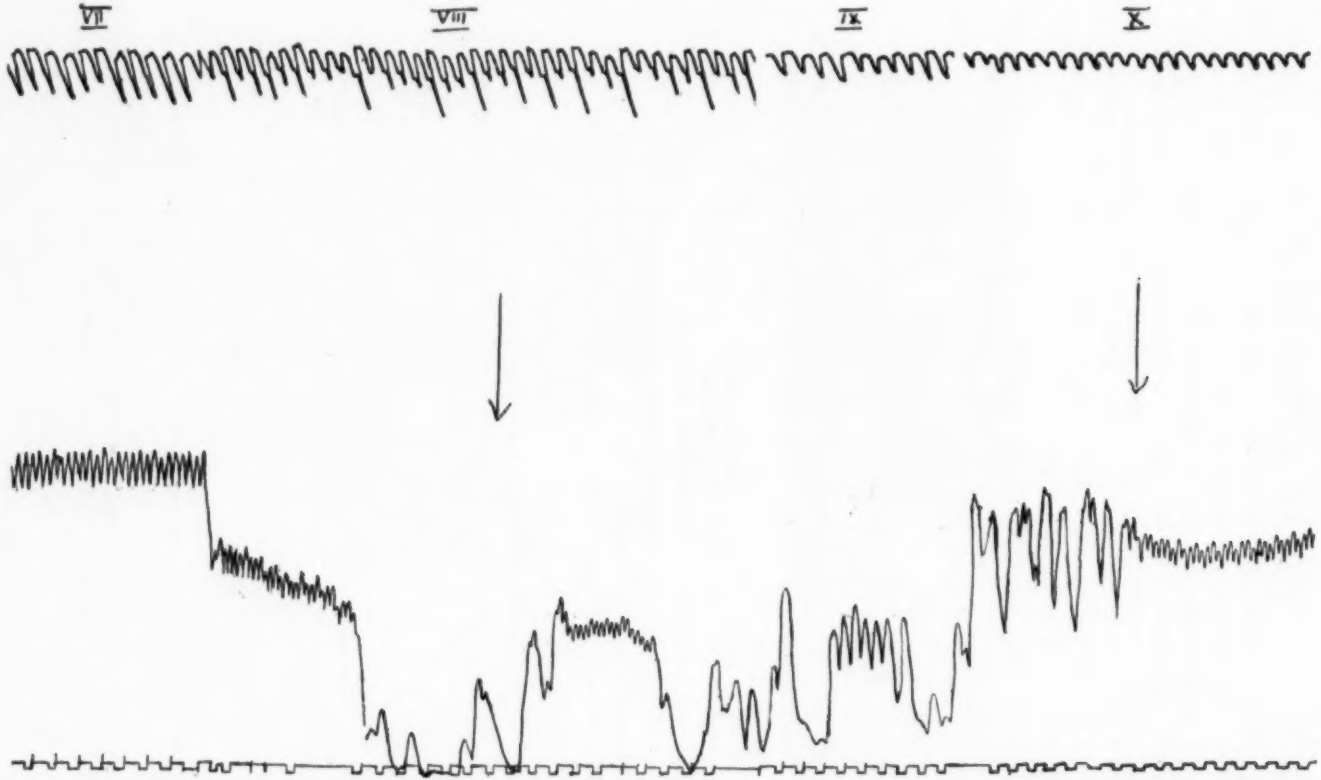

Fig. 6.—Dog. Weight, 10.2 kg. Intravenous injection ended at first arrow. VII. Normal tracing. VIII and IX. Ventricular fibrillation. X. Spontaneous resumption of normal rhythm at point indicated by second arrow. Upper tracing records respirations.

In some of the animals a remarkable cardiac arrhythmia is observed. There is a sudden transition from the normal kymographic tracing to one showing wide, irregular sweeps (Figs. 5 and 6). An abrupt fall in blood pressure and death from acute cardiac dilatation may follow this irregularity, or the normal tracing, at a higher level, may be resumed (Figs. 5 and 6). Electrocardiographic studies have shown that this irregularity is due to a coarse type of ventricular fibrillation.[7] (Fig. 7).

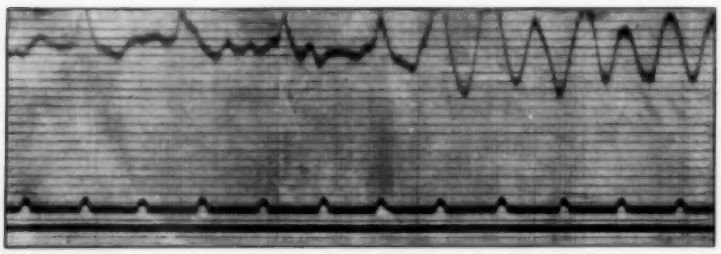

Fig. 7.—Dog. Weight, 8.6 kg. Received 2.75 gm. chloretone by stomach tube one hour prior to injection; 80 mg. in 5 c.c. salt solution intravenously injected (9.3 mg. per kg.). Electrocardiogram (taken by Dr. Bridgman) shows transition to coarse type of ventricular fibrillation.

In order that the mechanism of cardiac death might be observed, median thoracotomy was done in an animal receiving intratracheal anesthesia. There was at first generalized fibrillation of auricles and ventricles. The auricles then ceased to contract, becoming engorged

7. Ventricular fibrillation has been previously observed in experimental animals, but usually as a terminal event. Levy and Lewis have produced it in cats by administering low tensions of chloroform vapor together with small intravenous injections of adrenalin chlorid (Levy, A. G., and Lewis, T.: Heart, 1911-12, iii, 99). Levy, continuing these experiments, states that "spontaneous recovery in the cat is not infrequent; it may occur after a few seconds of fibrillation, or indeed after a period of one or more minutes. As a general rule, however, the heart neither recovers spontaneously nor can it be restored to its normal function by any method in general use for the treatment of cardiac syncope, and it eventually dies from asphyxia of its tissues" (Levy, A. G.: Heart, 1912-13, iv, 319).

In human beings, fibrillation of the ventricles has occurred either as a terminal phenomenon (Halsey, R. H.: Heart, 1915, vi, 67) or immediately after clinical death (Robinson, G. C.: Jour. Exper. Med., 1912, xvi, 291).

Lewis (Osler and McCrae's Modern Medicine, iv, 106) states: "Fibrillation in the ventricles . . . is similar to the condition of fibrillation in the auricles; when it comes, coördinate systole in the ventricle is suspended and the muscle exhibits a continuous quivering and ineffective movement. Its onset spells death. In animals under experimental conditions it is of extremely common occurrence; the circulation is immediately brought to a standstill, and the animal, after a few gasping respirations and twitching movements of asphyxial origin, remains perfectly quiescent."

Hoffman (Heart, 1911-12, iii, 213) has observed in a woman, recovery from fibrillation of the ventricles which lasted for two seconds at the end of an attack of paroxysmal tachycardia.

and dilated. The ventricles continued to fibrillate for a time; finally only the left ventricle near the apex of the heart continued in this fashion. Fibrillary contractions persisted for five or ten minutes after the heart had ceased beating. In several instances, especially in cats, the heart of the animal, studied immediately after death, continued to fibrillate for as long as fifteen minutes. In a few, the left ventricle was found firmly contracted in systole, the right flabby and dilated.

There is no significant change in respiration (Figs. 2 and 6) until just before death. Then there are asphyxial gasps at long intervals. Artificial respiration is unavailing in restoring the heart when once it has ceased to beat. Usually heart and respiration stop practically synchronously (Figs. 2 and 8).

Cutting the vagi before or after the injection produced no effect in the response (Fig 8).

3. *Pathological Changes.—In dogs,* the characteristic lesion is an inflammation of the gastro-intestinal tract. The earliest change is observed in an animal acutely poisoned by intravenous injection and dying at the end of about an hour. There is well-defined injection and swelling of the mucous membrane of the small intestine, especially of the ileum. When death occurs within a few minutes the heart is found tremendously dilated, in diastolic standstill. Where smaller quantities are injected intravenously, or daily subcutaneous injections are given over a longer period, and the animal survives for twenty-four hours or more, there is a severe gastro-enteritis, often hemorrhagic in character. The mucous membrane of the intestine is swollen, its vessels are engorged and a mucopurulent exudate may cover portions of its surface. Submucous ecchymoses are not uncommon. The ileum appears to suffer most, although the entire gastro-intestinal tract, "from cardia to anus," is sometimes filled with a bloody, mucoid material. In two animals several sharply-defined, punched-out ulcers were present in the duodenum and upper jejunum.

Microscopically,[8] there is marked congestion and edema of the mucosa; submucosa and muscularis present similar but less marked changes. The adjacent mesenteric fat may be congested and swollen.

All the abdominal organs are engorged with blood. The liver and kidneys, both grossly and microscopically, show congestion and cloudy swelling. A few small hemorrhages are sometimes observed in the renal medulla. In one instance the entire head of the pancreas was surrounded and infiltrated by extravasated blood, which under the microscope was seen to have forced its way between the lobules. In this same animal there was a subcapsular hemorrhage into the cortex of the kidney. Bronchopneumonia and pulmonary edema each were observed twice in association with the usual intestinal lesions.

8. We are indebted to Dr. T. P. Sprunt for notes on the microscopic pathology.

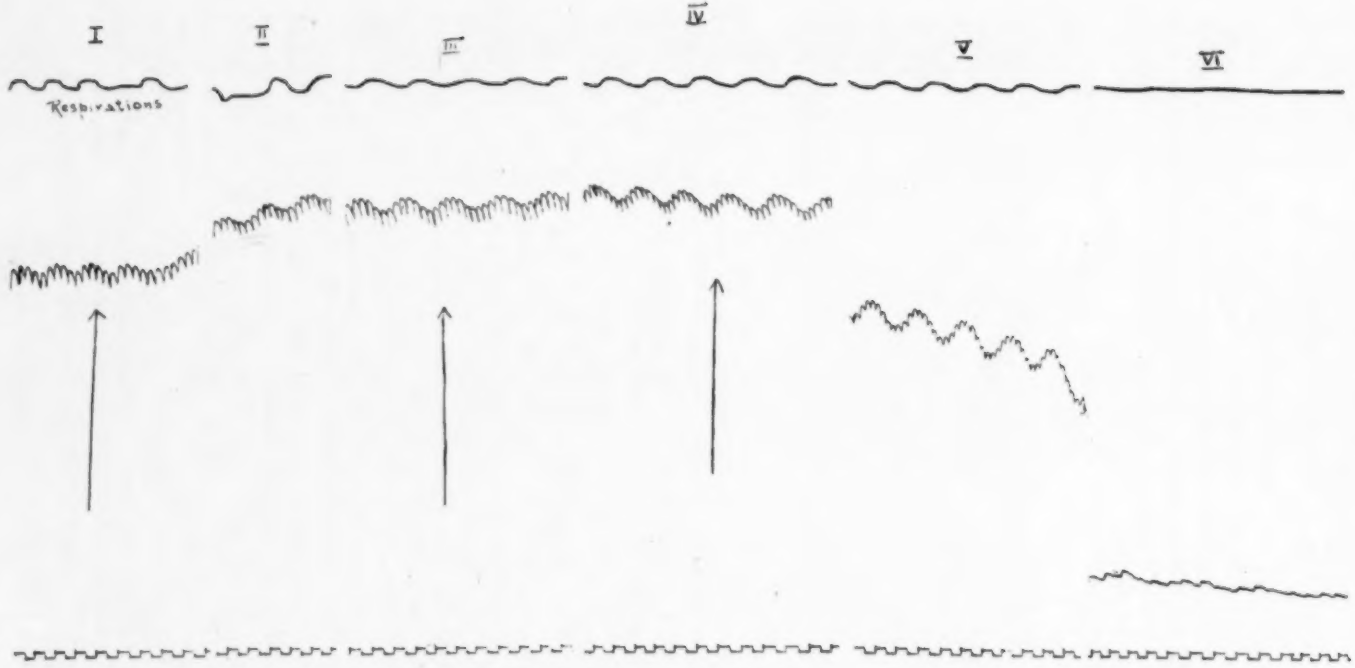

Fig. 8.—Cat. Weight, 3.65 kg. Cutting of vagi, followed by intravenous injection of 22 mg. in 3 c.c. saline. (6.02 mg. per kg.) I. Arrow indicates cutting of left vagus. II. Thirty seconds later. III. One minute later. Arrow indicates cutting of right vagus. IV. Two minutes later. Injection begun at arrow; duration, 45 seconds. V. One minute later. VI. One and one-half minutes later.

In *cats and rabbits*, pathological changes are slight and inconstant. There is generally some injection of the vessels of the upper portion of the small bowel. The liver and kidneys are congested, and in slowly poisoned animals show cloudy swelling. In one cat, hemorrhage occurred in the cecal region; in another there was a mild grade of pulmonary edema.

The tendency for rabbits poisoned by emetin occasionally to develop hemorrhagic pulmonary lesions has been noted by a number of previous observers. This has been confirmed by finding in one of our animals a patchy, hemorrhagic bronchopneumonia with actual bleeding into the lung tissue. Microscopically, there could be seen several points of rupture in the smaller arteries of the lung, from which blood was pouring into the alveoli.

4. *Effect on the Coagulation of the Blood.*—It was noted that the blood of poisoned animals clotted unusually slowly and that the clot was nonretractile in character. Several specimens of blood were examined by Professor Howell, who has very kindly made the following notes:

Dog 1.—Weight, 10 kg. Given 45 mg. emetin hydrochlorid subcutaneously. On the following day, profuse, bloody diarrhea and vomiting. Death on third day. Blood for examination taken on second day; collected in oxalate solution; plasma yellowish.

The oxalated plasma with thrombin solutions gave a clear, solid clot which was entirely nonretractile, having the same soft, jelly-like consistency that is obtained in blood to which Na_2CO_3 has been added to distinct alkaline reaction. This plasma, tested with neutral red, gave a reaction toward the acid side. Under the ultramicroscope,[9] the clot showed no visible structure whatever, whereas, the normal clot shows a mass of interlacing needles or spicules.

Dog 24.—Weight, 14.5 kg. Received 60 mg. emetin hydrochlorid intravenously. Died in thirty hours with a hemorrhagic gastro-enteritis.

A specimen of blood was taken immediately after death, oxalated and centrifugalized. Plasma very scanty in amount (about half normal) and yellowish in color. When thrombin solutions were added, clotting was slow and imperfect, as though fibrinogen were deficient in amount. The final result was a floating clot.

Under the ultramicroscope some fibrin needles formed but were scanty—scattered needles or small clumps of needles in place of the thickly meshed needles of normal plasma.

5. *Studies of Renal Function and Acidosis.*—Several dogs were used for this purpose. Albuminuria occurred inconstantly in slowly poisoned animals. There was no appreciable reduction in 'phthalein excretion, nor was there any nitrogen retention as evidenced by the urea content of the blood, even on the day preceding death. As a terminal phenomenon, on the day of death there was noted very slight increase

9. In this connection see article by Prof. Howell: Amer. Jour. Physiol., 1914, xxxv, 143.

in the hydrogen-ion concentration of the blood serum, but no change in that of the whole blood.[10] The CO_2 tension of the alveolar air was also somewhat lowered, in one animal falling to 33 mm. Hg several hours before death. This phenomenon has been noted by Meyer and Williams[11] in experimental emetin poisoning.

SUMMARY OF PREVIOUS EXPERIMENTAL WORK ON EMETIN

In 1817, Magendie and Pelletier[12] announced that they had isolated an emetic substance (*"matière vomitive"*) from the plant *psychotria emetica.* This substance they called emetin. They found that it had an emetic and purgative action and that it possessed marked narcotic properties when given to animals. In order to determine the toxicity of the drug, 10 grains were given to a dog. Vomiting and stupor followed, and the animal died in fifteen hours. "Anatomical examination showed that the animal had succumbed to a violent inflammation of the tissue of the lungs and of the mucous membrane of the intestinal tract, from cardia to anus." After obtaining similar effects with a number of animals, they concluded that "these observations are important, inasmuch as they show that emetin, given in large doses, may produce grave results."

During the remainder of the nineteenth century, a number of investigators undertook the study of ipecacuanha and its newly discovered alkaloid. Especially notable for their completeness and accuracy of observation are the articles of Dyce Duckworth[13] and Podwyssotzki.[14] The latter noted with wonder the cardiac arrhythmia which we have shown to be due to ventricular fibrillation.

Of fundamental importance was the work of Paul and Cownley[15] in 1893, demonstrating that the so-called emetin of previous workers was in reality a mixture of two alkaloids—the one, emetin, an amorphous substance, to which they assigned the formula $C_{15}H_{22}NO_2$; the other, which they named cephaëlin, a crystallin substance having the formula $C_{15}H_{22}NO_2$. Emetin hydrochlorid, $C_{15}H_{22}NO_2.HCl$, they were able to make in crystallin form. The presence of a third alkaloid, psychotrin, was determined by them two years later.[16] It was isolated in small amounts as lemon-yellow, rhombic prisms. The amount of alkaloids in ipecacuanha they found to be about 2 per cent.

Wild[17] in 1895, working for the first time with these pure alkaloids, which he obtained from Paul, investigated and compared their pharmacological action. He found that both emetin and cephaëlin are emetics, the emetic dose of the latter being half that of emetin. Both lower the blood pressure. The depression produced by the emetic dose of cephaëlin is less than that produced by the larger emetic dose of emetin. The vascular effects from emetin are greater. Both produce weakening, slowing and diastolic arrest of the heart.

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10. In making these determinations, the method recently described by Levy, Rowntree and Marriott was employed (THE ARCHIVES INT. MED., 1915, xvi, 389).

11. Meyer and Williams: Arch. f. exper. Path. u. Pharmakol., 1881, xiii, 70.

12. Magendie and Pelletier: Jour. de pharm., 1817, iii, 145.

13. Duckworth, Dyce: St. Bartholomew's Hosp. Rep., 1869, v, 218; also 1871, vii, 91.

14. Podwyssotzki: Arch. f. exper. Path. u. Pharmakol., 1879, xi, 231.

15. Paul, H. B., and Cownley, A. J.: Pharm. Jour. and Trans., 1893, liii, 61; also 1894, liv, iii.

16. Paul, H. B., and Cownley, A. J.: Pharm. Jour. and Trans., 1895, liv, 690.

17. Wild, R. B.: Lancet, London, 1895, lxxiii, 1274.

Lowin[18] in 1902, in a review of previous work on the subject, gives a complete bibliography to date. In addition to the facts emphasized by Wild, he confirms the characteristic gastro-intestinal lesions found by others in poisoned animals, and states that on the lungs emetin has no action, whereas, in cephaëlin poisoning, extravasation of blood into the lungs was noted several times. Deleterious action on the kidneys is found to be more characteristic of cephaëlin. Poisoned animals die of cardiac paralysis. Emetin, however, injures the heart in much smaller doses than does cephaëlin; but cephaëlin causes a greater fall in blood pressure.

The mode of excretion of the alkaloids could not be determined by Lowin. No trace of them was found in gastric or intestinal contents or in the urine.[19] Finally, he determined that psychotrin need not be considered in taking into account the action of these alkaloids; it is present in very small amounts, has no emetic action and no toxic action on the heart.

Our pharmacological and pathological findings are quite in accord with those of previous investigators, while two new facts are contributed. First, by electrocardiographic studies it has been shown that the cardiac irregularity produced in emetin poisoning is due to fibrillation of the ventricles, from which the animals may recover; and, second, Professor Howell's observations have shown alterations in the clotting properties of the blood.

ILL EFFECTS FOLLOWING THE CLINICAL USE OF EMETIN

That the therapeutic administration of emetin should not be regarded as an altogether innocuous procedure has been previously noted. Thus, even as early as 1895, Wild[17] says: "The fact that a dilution of 1 in 20,000 caused diastolic arrest of the frog's heart in forty-six minutes, renders caution necessary in giving larger doses of the alkaloid."

Baermann and Heinemann[8] have noted distressing and even alarming symptoms following doses much larger than are usually employed. They say: "Subcutaneous injections produce in some instances . . . slight general malaise; otherwise, with small and moderate sized doses of 60 to 150 mg., there are no symptoms. If 120 to 150 mg. are given in daily repeated injections, there appear, after three or four injections, malaise, lassitude, slight vertigo and loss of appetite. These symptoms disappear in from 24 to 72 hours after the emetin has been discontinued.

"Intravenous injections of 60 to 200 mg. cause no serious disturbance; there is slight vertigo, transient flushing of the face and retching. If this dosage is exceeded and 300 to 400 mg. are injected, serious symptoms are observed. These appear in from two to five minutes after the injection and consist of general vascular paralysis, severe expiratory dyspnea with cessation of respiration, loss of consciousness with vomiting, the passage of thin stools, and great slowing of the pulse. Although these phenomena are transient and are quickly

18. Lowin, C.: Arch. internat. de pharmacod. et de thérap., 1902, xi, 9.

19. More recently, Lyons (New Orleans Med. and Surg. Jour., 1912, lxiv, 884), using sterilized fecal filtrates made from the stools of individuals receiving ipecac by mouth, could demonstrate no amebicidal properties, in vitro, of the contents of the bowel.

TABLE 3.—Reported Cases in Which Ill Effects Followed the Clinical Use of Emetin

Case No.	Observer	Dosage and Mode of Administration	Total Dosage	Symptoms	Remarks
1	Allen[1]	4 gr. subcutaneously	4 gr.	Nausea for several hours; vomiting once, four hours after injection	Prompt recovery.
2	Chauffard[2]	100 mg. in 1 liter of water as rectal irrigation; patient had previously received subcutaneous emetin medication	100 mg. (1⅝ gr.)	Tremendous diarrhea same day—15 dysenteric stools, containing mucus and blood	Patient was having only two or three stools daily when irrigation was given; no further symptoms.
3	Spehl and Colard[3]	30 mg. twice a day for six days, followed by 30 mg. three times a day for 13 (?) days	1.17 gm. (19.5 gr.)	Lassitude followed four days later by flaccid paralysis of all muscles; difficulty in chewing, swallowing and articulating; heart rapid and beating feebly; volume of urine normal; no albuminuria, but diminution in amount of urea and chlorids excreted; temperature normal; cutaneous and deep reflexes present but diminished; face edematous	Condition very alarming; paralysis of muscles of respiration was feared; improvement began ten days after onset of symptoms; practically complete recovery in two weeks.
4	Eshleman[4]	1 gr. subcutaneously twice a day for five or six days	5-6 gr.	Purpuric eruption consisting of dark red, discrete patches; terrific peripheral neuritis, involving chiefly legs; arms only slightly affected; edema of legs; patellar reflexes absent	Eruption persisted for six weeks; neuritis gradually subsided.
5 and 6	Weis[5] (2 cases)	Not stated		Peripheral neuritis.	
7	Lyons[6]	⅓ gr. subcutaneously and ⅓ gr. by mouth twice a day for two days (t.o., 1⅓ gr. daily)	2⅔ gr.	Abdominal discomfort; diarrhea	Symptoms disappeared on stopping the drug by mouth.
8	Lyons[6]	1 gr. subcutaneously daily for two weeks, then 1 gr. by mouth daily for ten days	24 gr.	Diarrhea, emaciation, weakness; blood, pus and mucus in stools but no amebas	Slow recovery.
9	Lyons[6]	⅓ gr. subcutaneously daily for three days; then 2 gr. daily for four days	9 gr.	On fourth day, diarrhea and abdominal discomfort; no amebas in stools	Bowel disturbance disappeared in two or three weeks.

10	Lyons[6]	1 gr. subcutaneously for twelve days	12 gr.	Diarrhea; stools contained bloody mucus and a few resting amebas	Emetin stopped; saline enemas for five days, followed by another short course of emetin by needle, after which stools became normal.
11	Lyons[6]	1½ gr. subcutaneously daily for sixteen days	21½ gr.	Mild peripheral neuritis in legs; some general muscular weakness	Neuritis gradually cleared up.
12	Hume[7]	⅔ gr. twice a day for seven days, subcutaneously for a few days, then intravenously; ten days' rest, then ⅓ gr. daily subcutaneously for seven days	12⅝ gr.	Peripheral neuritis, with double wrist and foot drop	When seen six months later, was just recovering use of hands and feet.
13 to 18	Hume[7] (6 cases)	Not known		Peripheral neuritis, resembling beriberi	These cases occurred in a series of 100 cases of amebic dysentery treated with emetin. All cleared up on discontinuing the emetin.
19	Levy and Rowntree	½ gr. subcutaneously three times a day for nine days, then ⅓ gr. three times a day for two days, followed by ½ gr. three times a day for nine days	29 gr.	Diarrhea; muscular weakness; evidence of acute renal insufficiency with nitrogen retention and low phthalein output; death	Necropsy showed chronic passive congestion of viscera, a few ecchymoses in the pelves of the kidneys, with very slight distortion of the cortical striations, and bronchopneumonia.
20	Levy and Rowntree	½ gr. subcutaneously daily for four days	2 gr.	Diarrhea with blood and pus in the stools; development of toxic delirious state	Emetin administered to a rather anemic, poorly nourished patient for pyorrhea alveolaris; recovered in two weeks.

1. Allen: Jour. Am. Med. Assn., 1913, lx, 664.

Chauffard: Presse méd., 1913, xxi, 521. Chauffard's rectal irrigation with 100 mg. of emetin in 1 liter of water proved disastrous (Case 2). In the wards of the Johns Hopkins Hospital, high enemata of emetin (15 mg. in 250 c.c. of water) have not produced irritation. In several instances, effectual bowel movements were obtained in constipated individuals. It is possible that purgative enemata of emetin may prove to be of some value as an aid in the treatment of constipation. Rectal irrigations with solutions more dilute than those employed by Chauffard deserve further trial in amebic infections.

3. Spehl and Colard: Province méd., 1914, xxvii, 176. (Abstract.)
4. Eshleman: Bull. of Touro Infirmary, New Orleans Med. and Surg. Jour., 1914, lxvi, 965.
5. Weis: Ibid. (Note 4.)
6. Lyons: Am. Jour. Med. Sc., 1915, cl, 97.
7. Hume: Personal communication. Dr. E. H. Hume of the Yale Medical College, China, has kindly permitted us to cite these cases. They are to be reported shortly in the China Medical Journal.

relieved by suitable measures, yet on the basis of these observations we would regard as the maximal intravenous dose 250 mg. per kg. of body weight. We have never observed any injury to the kidneys, nor has there been any permanent damage to the patient, even with the high intravenous doses."

Vedder's[8] comments in this connection are worth quoting in full. He says: "Since emetin, by many observers, has been regarded as a more or less harmless drug, and since I am of the opinion that the doses used by some, and particularly by Baermann and Heinemann, are too large, I wish to point out the possible danger in not using due caution in the use of this very potent remedy.

"It would appear from our experimental observations that the doses proposed by Baermann and Heinemann are far too large, and that if the drug is administered in such doses, fatalities will soon occur which will unjustly discredit the use of emetin. Furthermore, these tremendous doses appear to be entirely uncalled for, since success is commonly obtained in the treatment of amebic dysentery and hepatic abscess with doses not exceeding 1 grain hypodermically.

"After seeing rabbits die immediately after intravenous injections of comparatively small amounts (from 3 to 5 mg.) of emetin hydrochlorid, *I should hesitate before administering even 1 grain intravenously in a human case.*[20] If given to one of the patients so susceptible to the effects of ipecac mentioned by Sollmann[21] such a treatment would not improbably be followed by death."

Lyons[22] from clinical observations warns against the use of large doses, as follows: "Too large doses or too prolonged use of moderate doses may cause a diarrhea or be responsible for its persistence. *There is increasing evidence that large doses of emetin are not without ill effect.*"[20]

The reported cases in which ill effects have followed the clinical use of emetin are given in the accompanying table (Table 3).

The experience of Lyons[22] with the administration of emetin by mouth precludes its use by the oral route. He found it exceedingly irritant even in small doses. Nausea, vomiting, griping, purgation and persistent abdominal discomfort followed the ingestion of 1/2 gr. in solution.

The case reported in detail earlier in this paper is the first in which the fatal result can be attributed to the therapeutic use of emetin. Only one fatal case of ipecacuanha poisoning could be found in the literature.[23]

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20. Italics ours.

21. Sollmann, T.: Text Book of Pharmacol., p. 309. (Cited by Vedder.) "Some persons are so sensitive to the local action of ipecac that the opening of a jar at a distance of several feet will produce violent sneezing and discomfort."

22. Lyons, R.: Am. Jour. Med. Sc., 1915, cl, 97.

23. Harrison (Lancet, London, 1908, ii, 536) tells of a 20-year-old youth who "drank several inches of a bottle of vinum ipecacuanhae." One hour after swallowing this dose there was uncontrollable vomiting and a rapid pulse; the extremities became cold and damp with perspiration. Death occurred in an hour and a half. At necropsy there was found subacute congestion of the stomach and first two feet of the intestine. The heart was in diastole. The other organs were normal. Harrison comments that "the congestion of the stomach was certainly an insufficient cause of death."

SUGGESTIONS WITH REGARD TO A RATIONAL EMETIN THERAPY

How may the toxic effects of emetin best be avoided? As the result both of clinical and laboratory observations the following suggestions are presented:

1. The administration of emetin hydrochlorid is not to be regarded as a harmless procedure. Even in therapeutic doses ill effects may follow its use.

2. Individualization by close clinical observation is essential both for the success and safety of the treatment. Patients may differ markedly in their susceptibility to the drug, and the various commercial preparations vary widely in toxicity. These points are strikingly demonstrated by the toxicity experiments herein reported.

3. The treatment should be given in courses, at intervals of several days or a week. The subcutaneous route is the one of choice. Individual dosage and the duration of each course must be determined by the exigencies of the case. One-third grain three times a day for a week or ten days is usually a safe dosage in amebic infections. It is rarely necessary to give more than 1½ grains daily. In the treatment of pyorrhea, Bass and Johns[24] advocate ½ grain daily for from three to six days, and maintain that no case need have more than six days' treatment. Under ordinary circumstances this seems well within the margin of safety. It must be borne in mind, however, that the administration of even relatively small doses over a long period of time may prove harmful.

4. The large dosage advocated by Baermann and Heinemann is unnecessary and dangerous.

5. Intravenous injections should be employed only in extreme cases. If this mode of administration seems imperative, small doses, well diluted (½ grain in 100 c.c. salt solution) should be slowly given, and the blood pressure should be carefully observed during the injection.

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24. Bass, C. C., and Johns, F. M.: Jour. Am. Med. Assn., 1915, lxiv, 553.

THREE CASES OF PURPURA HEMORRHAGICA IN CHRONIC TUBERCULOSIS

WITH A BRIEF REVIEW *

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The subject of purpura in this paper is treated from the standpoint of the relationship it bears to tuberculosis.

Several writers within the last two centuries have made observations on this phenomenon, endeavoring to find its cause and effect, and to discover the relation purpura has to other diseases with which it is associated.

Mackenzie[1] says:

> The great variety of supposed causes or associated conditions is sufficiently striking. Still more so is the fact that in one-third of 200 cases no explanation was offered for the purpura, though in several of the cases a necropsy was made. It will thus be seen how extremely complex is the pathology of purpura. All we can do in the present state of our knowledge is to accumulate further information and to exhaust every means—histological, bacteriological and chemical—in the investigation of cases.

Osler[2] also maintains "that purpura is obscure, and is an interesting manifestation of which we know so much and at the same time so little."

We may safely say, however, that the purpura observed in the three cases herein reported shows a striking relation between it and chronic tuberculosis. We may also claim that purpura is not of obscure origin, but that it has a definite mechanicotoxic cause.

The following are observations made by various authors who have given attention to this subject.

Osler claims that "purpura hemorrhagica rarely occurs with tuberculosis, but a fatal case has been reported."

Dieulafoy[3] divides purpura into different groups according to the diseases with which it is associated, as follows:

1. The nervous, as in tabes, myelitis and cancer of the spine.
2. Medicinal, as in copaiba, belladonna, iodin and snake venom poisoning.
3. The rheumatoid, as in peliosis rheumatica of Schoenlein.
4. Infectious: variola, erysipelas, typhoid, septicemia, infective endocarditis and pyemia.
5. Necrotic purpura, as in gangrene.
6. Acute pulmonary tuberculosis.

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* Submitted for publication Dec. 4, 1915.

* From the Tuberculosis Department of the Montefiore Home and Hospital.

1. Allbutt's System of Medicine, vi.
2. Osler's Modern Medicine, iv.
3. Dieulafoy: Principles of Medicine.

Struempell[4] endeavors in his classification to show that purpura has its origin in an infection of some sort. Rosenow of Chicago holds the same view. Struempell claims that if rabbits are inoculated with the blood of a patient having purpura the animal will show similar cutaneous symptoms. This tends to show that whether it is in typhoid, septic endocarditis or rheumatic fever there is some bacillus or coccus that is the direct etiological factor.

Adami[5] attributes the causes of all purpura to a poison which acts on the endothelium of the smaller cutaneous vessels, producing fatty degeneration. It is the weakening and necrosis of these cells that would seem to precede the hemorrhage by rhexis or diapedesis which set up the purpura or ecchymosis.

Woodhead offers similar explanations of those of Adami.

Fig. 1.—Showing purpuric areas on arms of patient G. I. (Case 3).

Muir and Ritchie[6] claim that "in some cases of acute tuberculosis, when the bacilli become lodged in a capillary, the endothelial cells of its wall may proliferate, and thus a ring of nuclei may be seen round a small central thrombus."

Unna[7] acknowledges that from the information he received from others and from the results of his own wide experience, he fails to understand how a capillary hemorrhage is brought about. He claims that it is neither by the ordinary understood rhexis or diapedisis, that capillary hemorrhages are produced. There must be, he says, a specific cause or a "blind force" which renders these small cutaneous vessels

4. Struempell's Text Book on Medicine.
5. Adami's Principles of Pathology.
6. Muir and Ritchie: Manual of Bacteriology.
7. Unna: Histopathology of the Diseases of the Skin.

subject to hemorrhage. His arguments against the accepted theories regarding these purpurae are as follows:

1. The blood vessels of the skin are not disposed to hemorrhage.
2. The locus minoris resistantiae is in the subcutaneous vessels more than in the cutaneous.
3. The contention that bacteria are probably the cause of hemorrhage he disproves by the fact that in phlyctenosis streptogenes, the streptococci are found in the capillaries; the same is true of the disease known as pustulosis staphylococci, but they cause necrosis of the endothelium only and not bleeding.
4. In hyaline degeneration of the endothelium he says that it produces thickened walls but no fragility; therefore there is no chance for rupture.

Fig. 2.—Purpuric areas on legs of patient G. I. (Case 3).

5. He also tries to disprove the theory of Rayer, who found purpura after the right iliac vein was thrombosed, with the argument that in varicose veins the tone of the vessel helps dilatation, and never rupture.
6. The only condition of purpura in which he recognizes the complete degeneration of the vessel as being its immediate cause is in the vessel paralysis or antemortem vascular changes, where the vessel yields and ruptures.

Pratt, in Osler's Modern Medicine, among the many causes of purpura which we have already discovered, quotes a good many authorities

who have worked on this subject from the serological point of view. This work has been done mainly at the Johns Hopkins Hospital. According to the author the probable additional causes for purpura may be a lack of fibrinogen in the blood, or a fibrinolysin, because in many cases of purpura one finds the coagulation time delayed. The authors also found that in the case of any fatty degeneration of the liver (the yellow atrophy of the liver) the cells are destroyed, lack of fibrinogen is the result of these changes, thus aiding in producing this condition. The same is true of phosphorus poisoning, which acts similarly on the liver.

They also found the blood platelets diminished in purpura, and that there is usually a leukocytosis present. Unna repudiates this very strongly.

Ewing[8] claims that bacteria are found in some cases in the blood and these are isolated, as for instance: Letzeuck's *Bacillus purpura,* which is in turn produced in animals; *Streptococcus pyogenes* has been isolated in typical cases by Hanot and Luzet, Widal, Therese and Guarnieri; *Staphylococcus pyogenes aureus* has been isolated by Lebreton, Litton, Fischl, Adler, Lewis and Librestini; the *Pneumococcus lanceolatus* by Clause and Claudi.

Changes in blood were found by Carrere and Gilbert, who reported a mild case having 3,350,000 red cells, while in more severe cases the diminishing number is greater; the hemoglobin index was subnormal. They also found a leukocytosis.

Hayem[9] claims that there exists a retardation of the coagulation time, and a reduction of blood plates.

Ewing states that the clotting appeared to be abnormally rapid, as in the course of an hour the specimen in the hematocytometer, diluted 1:100 with 0.6 per cent. salt solution, became jelly-like. Grawitz has also found an increase in the coagulability of the blood in these cases, after repeated hemorrhages, but red cells were found rapidly diminishing, and leukocytes were normal or reduced in numbers.

Stelwagon[10] agrees with Ewing in saying that there exists a mechanico-bacterio-toxic and chemical cause of purpura. He maintains that there must be a hyperemia and rupture or diapedesis of the vessel to produce purpura.

Hayem, who claims that the retardation of coagulability of the blood is due to the diminution of platelets, and to their destruction brought about by intestinal toxemia; this phenomenon is also found in cachectic conditions, such as leukemia, nephritis, carcinoma and "tuber-

8. Ewing's Clinical Pathology of the Blood, 1903.

9. Hayem: Quoted in Am. Jour. Med. Sc., 1911, cxlii, by Mathew and Carpenter in Purpura Hemorrhagica.

10. Stelwagon's Diseases of the Skin, Ed. 7, 1915.

culosis with purpura, the toxic substances of which are likely to produce profound changes in the blood, which lead to the rapid disintegration of the vessel wall, or to the slower hyaline or fatty degeneration."

John M. Cruice[11] says:

> Bensaude and Rivet think that purpura is not infrequently associated with tuberculosis. Of their thirty-five cases of chronic purpura hemorrhagica, seven occurred in individuals undoubtedly tuberculous, and in individuals probably tuberculous. They say that in the presence of a purpura, particularly in the recurring or chronic form, when the cause is not apparent, the clinician should by all means in his power, look for some chronic tuberculous lesion, either of the lungs, of the glands, or some other part of the body.
>
> Brown says that purpura hemorrhagica rarely occurs in tuberculosis. In the last 1,000 cases at the Adirondack Cottage Sanitarium but three cases have occurred. This corresponds closely to my figures. Out of 1,626 ward patients at the Phipps Institute I was able to find only eight cases of purpura. Mackenzie, in 200 cases of purpura, found it associated with tuberculosis only four times. Pratt in 258 cases of purpura, both primary and secondary, found it associated with tuberculosis seven times.

Grenit attributes the cause of purpura to one of the following conditions:

1. Hepatic lesion.
2. Nervous injury.
3. Intoxication of some sort.
4. Bacteria.
5. Blood changes.

but offers no discussion or explanation thereof.

Howell[12] states that he found a great diminution in the prothrombin, as in hemophilia, which retards coagulation and does not affect the antithrombin substance.

In thrombosed vessels the prothrombin is not affected but the antithrombin is diminished. In purpura hemorrhagica neither is affected.

Gaucher[13] claims as follows:

> 1. Infective secondary purpura is met with in the course of infective diseases such as variola, scarlatina, measles, intermittent fever, pyemia, puerperal infection, ulcerative endocarditis, acute tuberculosis (of which purpura may be a premonitious phenomenon), diphtheria, enteric fever, typhus, plague, malignant jaundice, pneumonia, cerebrospinal meningitis, infective tonsillitis and gonorrhea.
>
> 2. Toxic purpura is due to the absorption of certain protein substances, but a certain predisposition is necessary for this to occur.

Herbert French[14] maintains that "General tuberculosis is not a common cause of purpura, and yet in a few instances extensive purpura has

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11. Cruice, John M.: The Incidence of Purpura in the Course of Chronic Tuberculosis, Am. Jour. Med. Sc., 1912, cxliv, 875.
12. Howell, W. H.: Condition of Blood in Hemophilia, Thrombosis and Purpura, THE ARCHIVES INT. MED., 1914, xiii, 76; absts. in Jour. Am. Med. Assn., 1914, lxii, 488.
13. Gaucher: Diseases of the Skin.
14. French, Herbert: An Index of Differential Diagnosis of Main Symptoms, William Wood & Co., New York.

been the first, and, for the time being, the only, symptom of an obscure illness which has ultimately turned out to be general tuberculosis. The patient has generally been a child, and the diagnosis has only been possible when the course of the case has been watched."

The following are the three cases which have come under observation within the last eight months. It is useless to say that they can be taken as a criterion to prove anything regarding the cause of pathogenesis of purpura, but they do show us that there is a definite interrelationship between it and tuberculosis, and possibly give a clue to its etiology.

REPORT OF CASES

CASE 1.—W. S., aged 29, carpenter, Russian.

The condition of the lungs Nov. 16, 1914, was as follows:

Right lung: Dulness of both superior and middle lobes anteriorly and posteriorly, with large cavity over the same area, and moist râles all over.

Left lung: Dulness of both superior and middle lobes anteriorly and posteriorly, with amphoric breathing over the same area, and moist râles all over.

From Dec. 12 to Dec. 29, 1914, the patient showed the following additional symptoms: edema over the ankles, marked dyspnea, cyanosis, slight epistaxis, abdominal pain and nausea.

Dec. 29, 1914, patient was awake until 3 o'clock in the morning, felt nauseated and vomited coffee-colored material three times. Bowels also moved three times during the night; stools were loose and watery in consistence. Patient vomited twice in the morning, a dark greenish fluid. On examination patient was found markedly prostrated. He did not complain of anything except marked weakness. Hemorrhagic spots covered both legs, over the anterior and lateral surfaces and posteriorly. Similar hemorrhagic outlines covered the upper third of both legs and lower third of both thighs. Some spots were also seen over parts of the buttocks. They were also distributed over the inner surfaces of both forearms and upward to the midpoint of the arms. These hemorrhagic spots were confluent and covered areas 4 to 6 inches in length and about 3 inches in width. They were of a deep bluish-red hue.

The mucous membranes and the conjunctivae were negative. The chest findings were the same as on previous examinations.

From Dec. 29, 1914, to Jan. 1, 1915, the patient persistently vomited dark greenish fluid. The greater curvature of the stomach was low, reaching midway between the pubes and umbilicus, and a splashing fluid was readily made out.

From Jan. 1 to Jan. 10, 1915, the patient complained for the first time of pain in the right knee, and in both elbow joints. The purpuric rash became paler, and gradually disappeared. The face was puffed.

From Jan. 10 to Jan. 14, 1915, the puffiness grew more marked, the purpuric rash reappeared over the legs. Examination of the urine revealed an excessive amount of albumin, and numerous casts of all kinds, including a few waxy casts, and many cylindroids.

From Jan. 14 to Jan. 16, 1915, the purpuric rash gradually disappeared again. The patient became very dyspneic and cyanosed; the pulse was rapid, feeble and irregular in force. The heart beat was irregular, and a blowing

systolic murmur was heard at the apex, which was not transmitted. The second pulmonic was accentuated.

Jan. 16, 1915, the patient's general condition was somewhat improved. He complained of hunger, and wished to be out of bed, but dyspnea was still marked. The pulse was small, feeble and irregular. The puffiness of face subsided. There was no edema of the extremities. At 11:15 a. m. the patient sat up, but suddenly fell back and expired.

The blood on repeated examinations showed an average leukocyte count of 8,000 to 12,000; red cells of 4,500,000 to 5,000,000, and neutrophils 70 per cent. The hemoglobin was an average of 75 per cent. The blood culture revealed nothing.

Case 2.—S. A., aged 28, draughtsman, American.

The condition of the lungs was as follows:

Right lung: Dulness anteriorly from apex to third interspace; posteriorly from apex to sixth spinal vertebra; also one stripe at the base. On auscultation was found bronchial breathing, with moist râles from apex to third interspace anteriorly; posteriorly bronchial breathing, with moist râles from apex to sixth vertebral spine; below that there was feeble breathing.

Left lung: There were crackles all over anteriorly; posteriorly there was dulness over the supraspinous fossa, and feeble breathing could be heard to the fifth vertebra. Below that there was hyperresonance.

An attempted artificial pneumothorax on the right side was without the desired result. May 8, 1915, the patient developed marked edema of the right lower extremity, which lasted for three days, and which was accompanied by pain in the leg. The third day his left foot became markedly edematous. There were no signs of abdominal fluid or enlargement of liver or spleen. On examination the patient showed signs of a spontaneous pneumothorax on the right side, with signs of the heart being pushed over to the left.

The roentgenogram showed that there was apparently a pneumothorax occupying the entire right thoracic cavity, pushing the collapsed right lung, as well as the mediastinum, completely to the left side.

About the left side nothing definite could be said, as it was markedly compressed and obscured by the mediastinum.

May 29, 1915, the patient was very dyspneic, showed pronounced cyanosis over the extremities, and complained of pain in swallowing. On examination evidence of fluid could be elicited at the base of the right chest, and 33 ounces of thin, turbid fluid, greenish in color, was obtained.

June 1, 1915, the general condition of the patient was very poor. There was tenderness all over the abdomen, especially over the liver, which was very large, and could be palpated as far as the umbilicus. He had also edema of the right lower extremity. His elbow and knee joints were tender. The patient showed a purpuric rash over the sacral region, over the right clavicle, anteriorly and posteriorly, over the right supraspinous fossa, and over the anterior portion of the right leg. These purpuric spots were of a deep bluish hue, which did not disappear on pressure, and which covered areas about 3 to 5 inches in length and 3 inches in width.

On five successive urinary examinations, before and after the appearance of the purpuric rash, no albumin could be found.

On two successive blood counts, before and after the appearance of the rash, the patient had an average of hemoglobin of 65 per cent.; red blood cells, 5,000,000; white blood cells, 6,000; polymorphonuclear cells, 84 per cent.; small and large mononuclear cells, 16 per cent. The blood culture was found negative, and no bacilli were found in the blood.

CASE 3.—G. I., aged 38, tailor, Russian.

The lung condition on admission was as follows:

Feb. 18, 1915, the right lung showed dulness over two upper lobes, anteriorly and posteriorly, with bronchovesicular breathing and moist râles; below that the note was hyperresonant.

The left lung showed dulness of the entire side, anteriorly and posteriorly, with bronchial breathing and moist râles all over.

April 7, 1915, the physical examination and fluoroscope showed symptoms and signs of complete right-sided pneumothorax; absent breath sound all over, except the upper third posteriorly, and orthopnea.

On inquiry the history given by the patient tells of a sudden onset at 10:30 p. m., April 5, 1915.

May 8, 1915, the patient developed a purpuric rash over the extensor and flexor surfaces of the right arm, up to the elbow, and a similar condition on the extensor surface of the left thigh. The next day the patient had a swelling of the right wrist, followed by vomiting of bile-colored mucus. This vomiting lasted for three days. The patient also had diarrhea and blood-tinged stool. He also developed edema of both feet. This condition remained unchanged until May 23, 1915, when the patient developed edema of lower extremities. The purpuric rash on the lower extremities became more confluent, and he complained of pain in the knee joint, and also dyspnea on slight exertion.

From Jan. 18 to May 5, 1915, patient's urine showed the presence of albumin, hyaline, finely granular and epithelial casts.

The blood picture before and after the onset of purpura showed that the systolic blood pressure averaged 106, and diastolic, 80; hemoglobin, 80 per cent.; red blood cells, 4,450,000; white blood cells, 8,000; neutrophils, 75 per cent.; small and large lymphocytes, 29 per cent. Blood culture negative. Coagulation time normal.

CONCLUSION

Clinically expressed, the purpura observed in our three cases can be grouped in the same category with the condition known as peliosis rheumatica of Schoenlein. All the patients complained of pain in the joints, which came on suddenly and simultaneously with the onset of the rash, and all the cutaneous hemorrhages were of the simple type, with the exception of a single case, in which the patient's stool showed traces of blood—evidently suggesting purpura hemorrhagica proper.

Pathologically, we cannot put our cases in one distinct type of purpura, because they show characteristics common to all the classes.

For instance, blood cultures were found negative for bacteria. The red blood cells averaged from 4,500,000 to 5,000,000; white blood cells averaged 6,000; neutrophils 80 per cent., hemoglobin averaged 65 per cent., blood platelets were normal. The time of coagulation was normal. They all had edema of the extremities; all had diarrhea; one, in addition, showed albumin and casts in his urine; another had bloody stools; they were all prostrated; all manifested symptoms of spontaneous pneumothorax, and all showed a rash on similar locations, almost similarly distributed; all were confluent, and did not disappear on pressure.

Therefore, the following are the facts which explain our claim:

1. According to Muir, though not found in our cases, the tubercle bacilli form colonies in the cutaneous vessels, where they act as an irritant.

2. The secreted or excreted tuberculous toxins contribute to the necrosis of the cutaneous vessels.

3. The serum extravasated into the dependent portions, either by pressure exerted on some vein or lymphatic vessel, or when this is directly due to nephritis, produces in turn a pressure on the cutaneous vessels, which may act as a mechanical factor.

4. In the later stages of pulmonary tuberculosis the viscera may undergo either hyaline, amyloid or fatty degeneration, which aids in disintegrating the endothelial cells of the blood vessels, producing necrosis of the endothelium, and rupture; the fibrinogen-forming cells in the liver are also destroyed by the morbid process, thereby producing diminution in the viscosity of the blood, and also delaying its coagulation.

To sum up: The blood picture found in our three cases does not correspond with that found by the various authors quoted in our review of the subject.

But we did find, in these three cases, sufficient factors to warrant us in claiming that there is a relationship between purpura and tuberculosis.

They all showed the symptoms of intestinal toxemia, of amyloid degeneration, of the mechanical factors, and of general toxemia.

As we have seen in our review, one writer would lay stress on one factor as being the cause of purpura, another would find a different cause. In our cases we found a few causes which strengthen our belief that purpura can be found more often in tuberculosis than has been reported.

I am indebted to Dr. M. Fishberg and Dr. S. Wachsmann for their aid, encouragement and courtesy in offering their material.

REMARKS ON B. WELCHII IN THE STOOLS OF PELLAGRINS *

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The object of this paper is to call attention to the presence of abnormally large numbers of organisms belonging to the *B. Welchii* group, which have been found in the stools of pellagrins and to inquire whether this organism may not possibly bear a causal relationship to the disease.

B. Welchii has been described by various investigators since first described by Welch and Nuttall[1] in 1892 as *B. aerogenes capsulatus*.

For a complete description of the organism, with bibliography, reference may be made to the excellent monograph by Simonds.[2]

The characteristics of *B. aerogenes capsulatus* (*B. Welchii*) are as follows: It is a large gram-positive, nonmotile, anaerobic bacillus, producing spores under certain conditions. It is capable of fermenting nearly all sugars, and starch, and grows best on mediums containing these substances. In direct smears from lesions caused by it a capsule may be demonstrated. It coagulates and ferments milk with the production of butyric acid, and produces butyric acid from all sugars and starch. It is practically ubiquitous in distribution, having been found in the intestinal tract of domestic animals, birds and man, in the soil, water and air and in meat, fish, milk, cheese and other foodstuffs. The pathogenicity for man is limited. The resistance to conditions unfavorable to its growth is slight. Free oxygen and organic acids in a strength of 4 per cent. cause cultures to die quickly. The spores withstand a temperature of 80 C. for fifteen minutes but are usually destroyed by boiling for fifteen minutes. Simonds found the production of agglutinins in rabbits difficult.

The chief point of interest in connection with *B. Welchii* is that while it is recognized as a common inhabitant of the human intestinal tract, certain dietetic errors may cause it to assume a rôle of pathologic importance.

Growth by cultural methods in the absence of sugar is extremely difficult. Similarly, as pointed out by Kendall and Day,[3] *B. Welchii* is of no pathologic importance in the intestinal tract unless there is

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1. Welch, W. H., and Nuttall, G. H. F.: Bull. Johns Hopkins Hosp., 1892, iii, 81.

2. Simonds, J. P.: Monograph 5, Rockefeller Institute of Medical Research.

present an excess of utilizable carbohydrates and a deficiency in organisms of the lactic acid group, which produce conditions inimical to its growth. These investigators in their work on children at the Boston Floating Hospital, found that the feeding of sugars in an intestinal infection by *B. Welchii* was contraindicated and rapidly caused an increase in the severity of the symptoms, the chief of which was diarrhea. By the withdrawal of sugars from the diet and the addition of lactic acid and lactic acid bacilli introduced in the form of buttermilk, the diarrhea stopped and *B. Welchii* in the stools decreased in number to normal.

In the early part of August, 1909, a large number of cases of pellagra were reported to the State Board of Health from the Peoria State Hospital at South Bartonville, Ill. The secretary of the board detailed me to assist in an investigation to be carried on in conjunction with one undertaken by the U. S. Army Medical Corps. The results of these investigations were published by the board in the Health Bulletin.[4] At that time *B. Welchii* was found in the mouths of some patients and in the stools of thirteen out of eighteen. The drinking water of the hospital was found to contain a gas-producing organism which, however, was lost in plating. This may have been *B. Welchii*. Conditions at the hospital at the time the water was examined were not favorable to the making of anaerobic cultures. No gas was produced by any of the organisms isolated by aerobic cultures.

In two cases of pellagra recently studied[5] an amount of fluid feces adhering to a straight platinum wire of 20 gauge immersed one-quarter inch produced stormy fermentation of milk in twelve hours after heating to 80 C. for fifteen minutes. This was due to the presence of *B. Welchii*.

McNeal and Allison[6] in a study on the bacteriology of the stools in pellagra reported the presence of *B. Welchii* in a number of cases. In one case in which the stools were examined during the acute manifestations of the disease they remark, "This would indicate the presence of *B. Welchii* in hundreds of thousands per milligram of feces." They also remark that the diagnosis of pellagra in this case is doubtful "as the discoloration on the hands gradually faded without desquamation." From personal observation I am of the opinion that this is not an unusual occurrence in pellagra. McNeal and Allison attached no

3. Kendall, A. I., and Day, A. A.: Boston Med. and Surg. Jour., 1910, 1911, 1912.

4. Bulletin Illinois State Board of Health, August, October, and November, 1909.

5. Courtesy of Dr. Charles B. Read, Peoria, Ill.

6. Report of the Pellagra Commission of the State of Illinois, November, 1911, p. 55.

unusual significance to *B. Welchii* as a possible cause of the diarrhea, so pronounced in pellagra.

As above mentioned, Kendall and Day have reported that one of the essential conditions for the production of pathogenicity of *B. Welchii* is a high carbohydrate diet. Hewes and Kendall[7] report investigations on diarrhea in adults which were characterized by the presence of large numbers of spores of *B. Welchii,* which became worse on carbohydrate diet and rapidly improved on a pure protein and buttermilk diet.

It is notable in this connection that during the epidemic of pellagra the dietary of the Peoria State Hospital was reported to the Secretary of the State Board of Health as being very deficient in proteins and especially in proteins of animal origin. Conditions favorable to the growth of *B. Welchii* were ideal.

The conclusions reached by Wussow and Grindley as the result of investigations on the dietaries of the state institutions, made for the pellagra commission were as follows:

> Measured by the quantities consumed by a group of average patients fifty-three in number, for a period of seven days, the general diet supplied per man per day was 73.51 gm. of protein, 444.34 gm. carbohydrates, 55.77 gm. fat, 2,568 calories of energy, and 23.23 gm. of mineral matter, of which 1.07 gm. was phosphorus. With the exception of protein and prosphorus these quantities are probably adequate.

They further conclude that since the protein intake "represents the average intake of a large number, some of whom were very likely receiving less than the average, an increase in the amount would seem desirable. A study of the distribution of the nutrients among the animal and vegetable foods shows that the diet is chiefly vegetable in nature, much more so than the average American dietary." This work was done at Peoria during the time indicated at the top of the fourth column of H. Douglas Singer's table, to be found in the same report, and herewith quoted, and therefore does not indicate the true conditions during the time of the epidemic.

Singer remarks "without wishing to draw any conclusions as to cause and effect" that "the number of cases of pellagra diminished at Peoria and Dunning coincidently with increased meat and have increased at Elgin with diminished meat."

The above observations were about to be submitted for publication when Goldberger, Waring and Willets[8] published the results of their investigations.

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7. Hewes, H. F., and Kendall, A. I.: Boston Med. and Surg. Jour., 1912, clxvi, 75.

8. Goldberger, Joseph, Waring, C. H., and Willets, D. G.: Pub. Health Rep., Oct. 22, 1915, p. 3117.

Their work is so important that it demands critical analysis. Commenting on the theory as to the communicability of pellagra, they observe that since nurses and attendants in institutions where pellagra is endemic do not acquire the disease although exposed to constant infection, the explanation of the phenomenon would be found in the difference in diet of the two groups of residents. They noted in one institution that meat or other animal protein food formed a relatively small part of the diet of those subject to pellagra, while the vegetable component was unusually large. Similar conditions were found at other institutions. In one of these seventy-nine cases of pellagra were observed during the spring and summer up to Sept. 15, 1914. In a second institution 130 cases were observed during the same period.

AVERAGE DAILY AMOUNT OF MEAT* IN OUNCES SUPPLIED TO EACH INDIVIDUAL INCLUDING BOTH PATIENTS AND EMPLOYEES† (SINGER)

	July 1907 to July 1908	July 1908 to July 1909	July 1909 to July 1910	July 1910 to July 1911	Average
Peoria	5.3	5.8	5.9	8.2	6.3
Anna	11.3	10.9	10.6	9.8	10.65
Chester	6.4	5.0	4.5	6.4	5.6
Elgin	7.1	7.7	6.9	5.9	6.9
Jacksonville	10.6	10.9	11.3	10.5	10.8
Kankakee	8.7	7.8	8.0	8.2	8.2
Watertown	8.2	7.9	8.4	8.3	8.2
Dunning	6.5	6.5	6.6	7.5	6.8

* Uncooked and undressed.
† Employees are fewer in number but receive relatively larger amounts than patients.

Hygienic and sanitary conditions at both institutions were poor, but were not changed. September 15 the diet of the inmates was improved by the addition of milk, eggs, meats and leguminous vegetables. The carbohydrate element was at the same time considerably diminished. It is to be noted that in April, 1915, buttermilk was added to the diet. They give no reason for this addition, which at first was furnished on alternate days to inmates over 12 years of age; later when a sufficient supply was obtainable it was served daily to all.

The results obtained were as follows:

In the first institution, of the 79 cases, 67 were under observation for one year. In none of them was there a recurrence of the disease. In the second institution, of the 130 cases, 105 were under observation for one year. In 1 case only was there a recurrence. None of the

nonpellagrin residents numbering, respectively, 99 and 69, developed the disease.

At the Georgia State Sanitarium, 72 pellagrins (36 colored and 36 white) out of 80 selected cases were under observation from not later than Dec. 31, 1914, up to Oct. 1, 1915. As at the other institutions, an increase was made in the protein food, syrup was entirely excluded and buttermilk was given twice daily. None of this group of 72 patients showed evidence of a recurrence at the end of the experiment.

During this period fifteen of thirty-two female pellagrins developed recurrences.

Goldberger and Wheeler[9] further to test the effect of diet in pellagra undertook to produce the disease experimentally in a group of non-pellagrous convicts. Of eleven volunteers who were fed for five months on a diet entirely free of animal protein, six developed a typical dermatitis and mild but distinct nervous and gastro-intestinal symptoms. It is to be regretted that these excellent studies did not include a study of the bacteriological flora of the feces before and after placing the patients on the test diet. The theory that *B. Welchii* alone or in symbiosis with another organism in the presence of an excess of carbohydrates, by the production either of butyric acid or a toxin, and their subsequent absorption may produce pellagra, is an attractive one. It harmonizes well with the infectious, toxic, and nutritional theories. It explains seasonal variations and the relation of poverty to pellagra. Poverty is usually associated with unhygienic, unsanitary living conditions, a high carbohydrate diet and a low animal protein diet as pointed out by Sydenstricker.[10]

SUMMARY

1. *B. Welchii* has been found with marked regularity in the stools of pellagrins in numbers greater than normal.

2. These pellagrins were on a dietary composed principally of vegetable foods high in carbohydrates.

3. The diet was extremely low in protein and especially in protein of animal origin.

4. Diarrhea is one of the most constant symptoms of the disease known as pellagra.

5. *B. Welchii* has been found to produce severe diarrhea in children and adults in the presence of a high carbohydrate diet.

6. The diarrhea caused by *B. Welchii* can be cured by a protein diet and buttermilk.

9. Goldberger, Joseph, and Wheeler, G. A.: Pub. Health Rep., Nov. 12, 1915, p. 3336.

10. Sydenstricker: Pub. Health Rep., Oct. 22, 1915, p. 3182.

7. Goldberger has prevented pellagra by the addition of proteins and buttermilk to the diet, and has experimentally caused pellagra by means of a pure carbohydrate diet.

8. Whether *B. Welchii* was present in the stools of Goldberger's cases in greatly increased numbers is not known.

The above facts by no means prove that *B. Welchii* is the direct or sole cause of pellagra, but their coincidence is sufficiently significant to justify further investigation.

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CORRECTION

Attention is called to the following corrections in article by Drs. Harold Schwartz and Caroline McGill in THE ARCHIVES for January, 1916:

Under Table 2, giving the normals of various authors, the values given refer to urea nitrogen, with the exception of the figures given by Rowntree and Fitz, Schondorff, Farr and Austin (0.43), Widal, Picard, Weill and Vallery-Radot, which refer to urea.

In the subject matter, reference to Tileston and Comfort, and Folin and Denis, refer to urea nitrogen.

Conclusion No. 1, the word "fasting" should be omitted.